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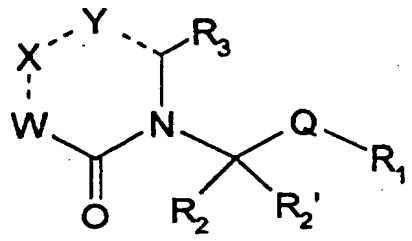
(54) Title: LACTAM INHIBITORS OF THROMBIN

(57) Abstract

This invention relates to heterocyclic inhibitors of the enzyme thrombin, their preparation, and pharmaceutical compositions thereof having general formula (I), wherein W, X, Y R_1 to R_3 are as defined herein. Also, the invention relates to the use of such compounds and compositions as anticoagulants and as agents for the treatment and prophylaxis of thrombotic disorders such as venous thrombosis, pulmonary embolism and arterial thrombosis resulting in acute ischemic events such as myocardial infarction or cerebral infarction.



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LACTAM INHIBITORS OF THROMBIN

FIELD OF THE INVENTION

This invention relates to compounds useful for the treatment of thrombotic disorders, and more particularly to novel lactam inhibitors of serine proteases such as factor VIIa, Xa and thrombin. This application is a continuation-in-part of USSN 60/025,599 and GB 9618687.9 filed 6 September 1996 incorporated herein by reference.

BACKGROUND

Inordinate thrombus formation on blood vessel walls precipitates acute cardiovascular disease states that are the chief cause of death in economically developed societies. Plasma proteins such as fibrinogen, proteases and cellular receptors participating in hemostasis have emerged as important factors that play a role in acute and chronic coronary disease as well as cerebral artery disease by contributing to the formation of thrombus or blood clots that effectively diminish normal blood flow and supply. Vascular aberrations stemming from primary pathologic states such as hypertension, rupture of atherosclerotic plaques or denuded endothelium, activate biochemical cascades that serve to respond and repair the injury site. Thrombin is a key regulatory enzyme in the coagulation cascade; it serves a pluralistic role as both a positive and negative feedback regulator. However, in pathologic conditions the former is amplified through catalytic activation of cofactors required for thrombin generation as well as activation of factor XIII necessary for fibrin cross-linking and stabilization.

In addition to its direct effect on hemostasis, thrombin exerts direct effects on diverse cell types that support and amplify pathogenesis of arterial thrombus disease. The enzyme is the strongest activator of platelets causing them to aggregate and release substances (e.g. ADP TXA_2 NE) that

further propagate the thrombotic cycle.

Platelets in a fibrin mesh comprise the principal framework of a white thrombus. Thrombin also exerts direct effects on endothelial cells causing release of vasoconstrictor substances and translocation of adhesion molecules that become sites for attachment of immune cells. In addition, the enzyme causes mitogenesis of smooth muscle cells and proliferation of fibroblasts.

The principal endogenous neutralizing factor for thrombin activity in mammals is antithrombin III (ATIII), a circulating plasma macroglobulin having low affinity for the enzyme. Heparin has shown clinical efficacy in alleviating venous thrombosis by enhancing ATIII/thrombin binding through catalysis. However, heparin also catalyzes inhibition of other proteases in the coagulation cascade and its efficacy in platelet-dependent thrombosis is largely reduced or abrogated due to inaccessibility of thrombus-bound enzyme. Also, adverse side effects such as thrombocytopenia, osteoporosis and triglyceridemia have been observed following prolonged treatment with heparin.

It has been proposed that thrombin activity can be inhibited by compounds that compete with fibrinogen for thrombin's catalytic site, thereby inhibiting proteolysis of that protein or other protein substrates such as the thrombin receptor. A common strategy for designing enzyme inhibitory compounds relies on mimicking the specificity inherent in the primary and secondary structure of the enzyme's natural substrate. Thrombin inhibitors have been modeled upon the partial sequence of the fibrinogen A α chain comprising its proteolytically susceptible region (Blomback, et al., J. Clin. Lab. Invest., 24, 59, 1969). This region of fibrinogen minimally includes the residues commencing with phenylalanine:

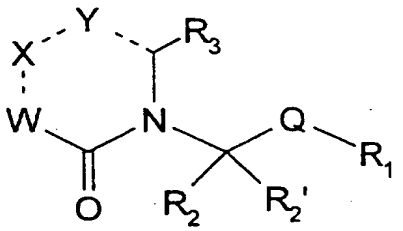
Ala-Asp-Ser-Gly-Glu-Gly-Asp-Phe-Leu-Ala-Glu-Gly
-Gly-Gly-Val-Arg-Gly-Pro-Arg
↑ scissile bond

Systematic replacement of amino acids within this region has led to optimization of the tripeptidyl inhibitory sequence exemplified by the peptide (D)-Phe-Pro-Arg which corresponds to interactions within the P_3-P_2-P_1 local binding sites on thrombin (Bajusz S. et al. in Peptides: Chemistry Structure and Biology: Proceedings of the Fourth American Peptide Symposium, Walter R., Meienhofer J. Eds. Ann Arbor Science Publishers Inc., Ann Arbor MI, 1975, pp. 603).

It is an object of the present invention to provide thrombin inhibitors that display inhibitory activity towards serine proteases such as factor VIIa, factor Xa and thrombin which may be used in the treatment or prophylaxis of thrombotic disorders.

SUMMARY OF THE INVENTION

The present invention provides novel compounds that are useful for inhibiting thrombin activity, represented by formula (I):



(I)

wherein:

W and **X** are independently selected from CH-R_4, C-R_4, N-R_4, N, O, S, SO and SO_2, provided that at least one of W and X is selected from N-R_4, N, O, S, SO and SO_2;

Y is selected from CH-R_4, C-R_4 and C=O;

Q is selected from carbonyl, C=S and CH-R_4;

R_1 is a polar amino acid residue or derivative or analogue

thereof optionally substituted with an amino acid, a peptide or a heterocycle;

R_2 and R_2' are independently selected from H, halogen, C_{1-16} alkyl optionally substituted with C_{6-16} aryl, heterocycle or a C_{3-7} cycloalkyl group; and

R_3 and R_4 are independently selected from H; NR_5R_6; carboxyl; C_{6-16} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-16} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_5R_6 or a C_{6-16} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, carboxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group; or

when Y is CH-R_4 or C-R_4 then R_3 and R_4 together with Y form a 5 or 6 member saturated or unsaturated carbocyclic ring;

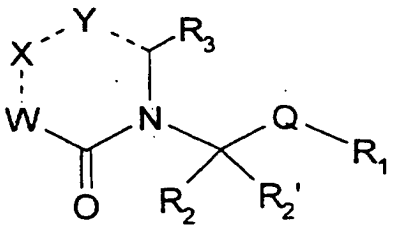
R_5 and R_6 are independently selected from H and C_{1-4} alkyl.

According to another aspect of the invention, there is provided pharmaceutical compositions comprising compounds of the formula (I) in combination with pharmaceutically acceptable carriers, diluents or adjuvants.

In yet another aspect, there is provided a method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to formula (I).

DETAILED DESCRIPTION OF THE INVENTION

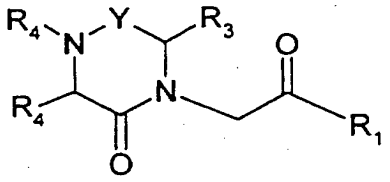
The present invention relates to compounds which inhibit the enzyme, thrombin. These molecules are characterized by a lactam moiety as illustrated in formula (I):



(I)

wherein W, X, Y, Q and R_1 to R_6 are as previously defined.

In a preferred embodiment, compounds of the invention are represented by formula (Ia):

Ia 

wherein Y, R_1, R_3 and R_4 are as previously defined.

The term "hydrophobic group" (HG) as used hereinafter, refers to any group which lacks affinity for, or displaces water. Hydrophobic groups include but are not limited to C_{1-20} alkyl, C_{2-20} alkenyl (e.g. vinyl, allyl) or C_{2-20} alkynyl (e.g. propargyl) optionally interrupted by a carbonyl group, (e.g. forming an acyl group); C_{6-16} aryl, C_{3-7} cycloalkyl, C_{6-20} aralkyl, C_{6-20} cycloalkyl substituted C_{1-20} alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group (e.g. forming an acyl group) and the ring portion is optionally substituted with C_{1-6} alkyl such as methyl ethyl or t-butyl; or a hydrophobic amino acid side chain. Preferred hydrophobic groups include cyclohexyl, benzyl, benzoyl, phenylmethyl, phenethyl and para-t-butyl-phenylmethyl.

The term "arginyl moiety" represents an arginine amino acid residue or an analogue or derivative thereof. For example, an analogue or derivative of the natural residue may incorporate a longer or shorter methylene chain from the alpha carbon (i.e. ethylene or butylene chain); replacement of the guanidino group with a hydrogen bond donating or accepting

group (i.e. amino, amidino or methoxy); replacement of the methylene chain with a constrained group (i.e. an aryl, cycloalkyl or heterocyclic ring); elimination of the terminal carboxyl (i.e. des-carboxy) or hydroxyl (i.e. an aldehyde); or a combination thereof.

The term "alkyl" represents a straight or branched, saturated or unsaturated chain having a specified total number of carbon atoms.

The term "aromatic" or "aryl" represents an unsaturated carbocyclic ring(s) of 6 to 16 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_5R_6) halogen or C_{1-6} alkyl. Aromatic rings include benzene, biphenyl, napthhalene, phenanthrene and anthracene. Preferred aromatic rings are benzene and naphthalene.

The term "cycloalkyl" represents a mono- or poly- (including bridged) carbocyclic ring of 3 to 7 carbon atoms which is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_5R_6), halogen, carboxy (and esters thereof) or C_{1-6} alkyl. Cycloalkyl groups are generally saturated but may be partially unsaturated and include cyclo-propyl, butyl, pentyl, hexyl and heptyl. A preferred cycloalkyl group is cyclohexyl.

The term "aralkyl" represents a substituent comprising an aryl moiety attached via an alkylene chain (e.g. benzyl, phenethyl) wherein the sum total of carbon atoms for the aryl moiety and the alkylene chain is as specified. The aryl or chain portion of the group is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_5R_6) halogen or C_{1-6} alkyl

The term "heteroatom" as used herein represents oxygen, nitrogen or sulfur (O, N or S) as well as sulfoxyl or sulfonyl (SO or SO_2) unless otherwise indicated. It is understood that alkyl chains interrupted by one or more heteroatoms means that a carbon atom of the chain is replaced with a heteroatom having the appropriate valency. Preferably, an alkyl chain is interrupted by 0 to 4 heteroatoms. Generally two adjacent

carbon atoms are not both replaced with a heteroatom except for example to form a sulfonamide group.

The term "heterocycle" represents a saturated or unsaturated mono- or polycyclic (i.e. bicyclic, bridged) ring incorporating 1 or more (i.e. 1-4) heteroatoms selected from N, O and S. It is understood that a heterocycle is optionally mono- or di-substituted with OH, SH, amino (i.e. NR_5R_6), halogen, CF_3, oxo or C_{1-6} alkyl. Examples of suitable monocyclic heterocycles include but are not limited to pyridine, piperidine, pyrazine, piperazine, pyrimidine, imidazole, thiazole, oxazole, furan, pyran and thiophene. Examples of suitable bicyclic heterocycles include but are not limited to indole, quinoline, isoquinoline, purine, and carbazole.

The term "hydrophobic amino acid" represents an amino acid residue that bears an alkyl or aryl group attached to the α-carbon atom. The alkyl or aryl group can be substituted, provided that the substituent or substituents do not detract from the overall hydrophobic character of the amino acid. Examples of hydrophobic amino acids include natural amino acid residues such as alanine; isoleucine; leucine; phenylalanine; and non-naturally occurring amino acids such as those described in "The Peptides", vol. 5, 1983, Academic Press, Chapter 6 by D.C. Roberts and F. Vellaccio. Suitable non-naturally occurring amino acids include cyclohexylalanine and 1-aminocyclohexane-carboxylic.

By "amino acid side chain" is meant the substituent attached to the carbon which is α to the amino group. For example, the side chain of the amino acid alanine is a methyl group while benzyl is the side chain for phenylalanine.

In a preferred embodiment of the invention, **W** is $CH-R_4$ or $C-R_4$ while **X** is $N-R_4$, N, O, S, SO or SO_2, wherein R_4 is as previously defined. More preferably, W is $CH-R_4$ or $C-R_4$ while

X is N-R_4 or N. More preferably, W is CH-R_4 while X is N-R_4. In an even more preferred embodiment, W is CH_2 while X is N-R_4.

Preferably, Y is CH-R_4 wherein R_4 is as previously defined. More preferably, Y is CH-R_4 wherein R_4 is H. In another preferred embodiment, Y is a carbonyl (C=O) group and more preferably Y is a C=O group when X is N-R_4 or N and most preferably when X is N-R_4 and W is CH_2.

Preferably Q is carbonyl (C=O).

Preferably R_2 and R_2' are independently H; halogen such as F or Cl; or C_{1-4} alkyl such as methyl or ethyl. More preferably, one of R_2 and R_2' is H. Most preferably, both R_2 and R_2' are both H.

Preferably, R_3 and R_4 are independently a carboxyl group or a hydrophobic group such as a saturated or unsaturated carbocycle of 5 or 6 members optionally fused to another carbocyclic group. The carboxyl group or hydrophobic group may be linked via a spacer such as a C_{1-16} alkyl chain optionally interrupted with 1 or more (i.e. 1-4) heteroatoms, carbonyl or sulfonyl (SO_2) groups. More preferably, only one R_4 substituent is an optionally substituted aromatic ring such as phenyl, biphenyl, cyclohexyl, indole, thienyl, quinoline, tetrahydroisoquinoline, naphthyl or benzodioxolane linked via C_{1-16} alkyl optionally interrupted with a heteroatom or sulfonyl or carbonyl; while R_3 is selected from H, C_{1-16} alkyl, and an optionally substituted aromatic ring linked via C_{1-16} alkyl. Optional aromatic ring substituents include OH, carboxyl (and esters thereof), C_{1-4} alkyl and halogen. Preferably R_3 is other than 3,5-bis(trifluoromethyl)benzoyl when R_4 is 3-indolylmethyl.

In another preferred embodiment, Y is -CH_2- or carbonyl and R_3 is H, saturated or unsaturated carbocycle or heterocycle of 5 or 6 members optionally fused to another carbocyclic group. The carbocycle or heterocycle group is optionally linked via a

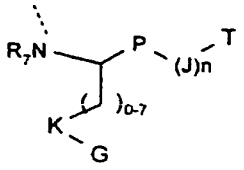
spacer such as a C_{1-16} alkyl chain optionally interrupted with 1 or more (i.e. 1-4) heteroatoms, carbonyl or sulfonyl (SO_2) groups. Particularly preferred R_3 groups include H, methyl, isopropyl, butyl, 2°butyl, benzyl (optionally substituted i.e. 2-Cl, 3-Cl, 4-Cl, 3,4-diCl, 4-methyl, 4-methoxy), cyclohexylmethyl, pyridinylmethyl, 2-naphthylmethyl, biphenylmethyl, phenethyl and $-CH_2-NH-SO_2-$benzyl. More preferably R_3 is H or optionally substituted benzyl and most preferably is benzyl optionally substituted i.e. 2-Cl, 3-Cl, 4-Cl, 3,4-diCl, 4-methyl, 4-methoxy.

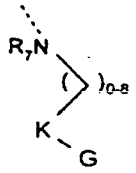
In another more preferred embodiment, R_3 and R_4 are independently an optionally substituted phenyl or cyclohexyl ring linked via C_{1-4} alkyl optionally interrupted with carbonyl or sulfonyl. In an even more preferred embodiment, one of the R_4 substituents is phenylpropionyl, phenylpropyl, benzylsulfonyl, 2,3-dichlorophenylpropionyl, phenylethyl or cyclohexyl-methyl while R_3 is H, isopropyl or benzyl.

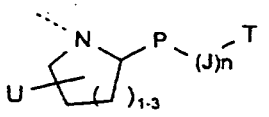
In an alternative embodiment, when Y is CH-R_4 or C-R_4 then R_3 and the R_4 from Y together form a 5 or 6 member saturated or unsaturated carbocyclic ring. Preferably said ring is a phenyl or cyclohexyl ring and more preferably a phenyl ring fused to the ring containing W, X and Y.

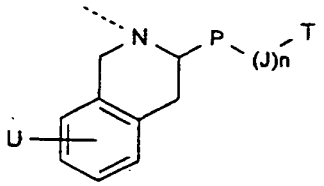
Preferably $\mathbf{R_5}$ and $\mathbf{R_6}$ are independently hydrogen, methyl or ethyl. More preferably R_5 and R_6 are independently hydrogen or methyl and most preferably are both hydrogen.

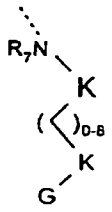
In a preferred embodiment, $\mathbf{R_1}$ is represented by one of formula IIa to IIe:

IIa 

IIb 

IIc 

IId 

IIe 

wherein:

R_7 is hydrogen or C_{1-6} alkyl;

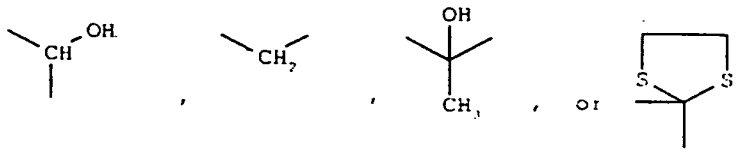
K is a bond or $-NR_7-$;

G is C_{1-4} alkoxy; cyano; $-NHR_8$; $-CH_2-NHR_8$; $-C(NH)-NHR_8$; $-NH-C(NH)-NHR_8$; $-CH_2-NH-C(NH)-NHR_8$; a C_{6-12} cycloalkyl or aryl substituted with cyano, $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NHR_8$, $-CH_2-NH-C(NH)-NHR_8$, halogen C_{1-4} alkyl, aryl or heterocycle; or a 5 or 6 member, saturated or unsaturated heterocycle or heterobicycle optionally substituted with cyano, $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NH_2$ $-CH_2-NH-C(NH)-NHR_8$, halogen C_{1-4} alkyl, aryl or heterocycle; provided that G is other than unsubstituted indole and when G is C_{6-12} cycloalkyl or aryl then G is substituted with at least one group selected from $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NHR_8$ or $-CH_2-NH-C(NH)-NHR_8$;

U is cyano, $-NHR_8$, $-C(NH)-NHR_8$ or $-NH-C(NH)-NHR_8$;

R_8 is H, OH or NH_2;

P is a bond, -C(O)-, -C(S)- or a bivalent group:



J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, $O-R_4$, carboxyl, amino, a peptide chain, C_{1-16} alkyl,

C_{1-16} alkoxy, C_{6-20} aralkyl, or heterocycle optionally substituted;

provided that R_1 is other than $-NHNH_2$.

When R_1 incorporates an amino acid or derivative of the formula IIa (wherein P is a carbonyl), the carbon atom alpha to the nitrogen may adopt one of two stereo configurations. In a prefered embodiment the alpha carbon will be oriented such that the amino acid or derivative will be in the L configuration.

Preferably R_7 is H or methyl and most preferably H.

Preferably **K** is a bond.

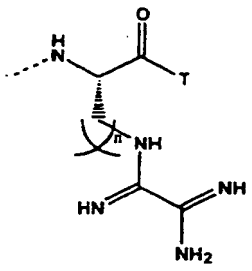
Preferably **G** is $-NH-C(NH)-NH_2$ attached via a methylene chain of 3-7 carbons; a phenyl or piperidine attached via a methylene chain of 0 to 3 carbons wherein the phenyl or piperidine is substituted with $-C(NH)-NH_2$; or cyclohexyl attached via a methylene chain of 0 to 3 carbons wherein the cyclohexyl is substituted with $-NH_2$. More preferably G is $-NH-C(NH)-NH_2$ attached via a methylene chain of 3 atoms. More preferably G is piperdin-3-yl N-substituted with $-C(N)-NH_2$.

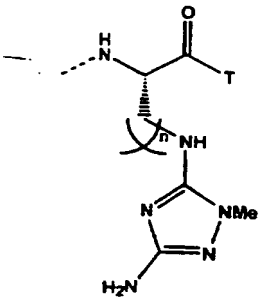
In another embodiment G is a piperidine ring attached via a methylene chain of 0-3 carbons wherein the piperidine ring is substituted with one or two of the groups selected from cyano, $-NH_2$, $-C(NH)-NH_2$, $-C(NH)-NH-NH_2$, $-C(NH)-NH-OH$ and $-NH-C(NH)-NH_2$. Preferably, the piperidine ring is attached via one methylene group at the 3 position of the ring. Preferably the ring is mono-substituted at the 1 position (the nitrogen atom) and is one of $-C(NH)-NH_2$, $-C(NH)-NH-NH_2$ or $-C(NH)-NH-NH-OH$. More preferably the substituent is $-C(NH)-NH_2$.

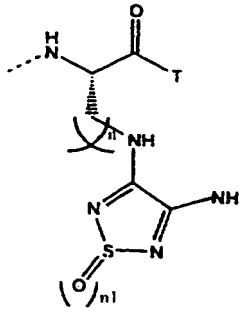
Preferably **P** is $-C(O)-$.

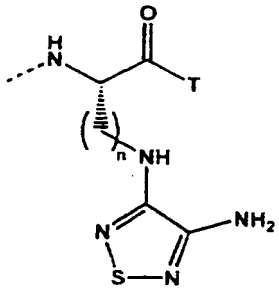
Preferably **J** is selected from: $-CH_2-S-CH_2-CH_2-$; $-CH_2-O-CH_2-CH_2-$; $-CH_2-NH-CH_2-CH_2-$; and a bond when n is 0. More preferably, J is a bond while n is 0.

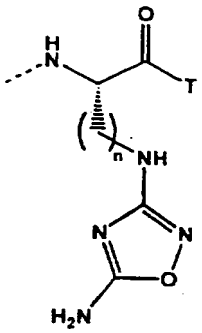
In particular embodiments of the invention, R_1 is selected from the following amino acid derivatives prepared according to the procedures described in Bioorg. Med. Chem., 1995, 3:1145 and PCT application WO 96/19483 (published 27 June 1996) incorporated herein by reference.

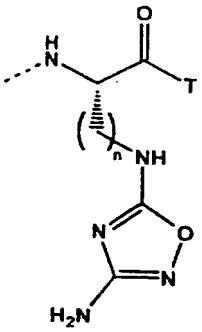


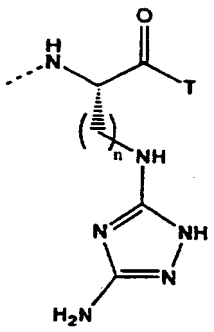


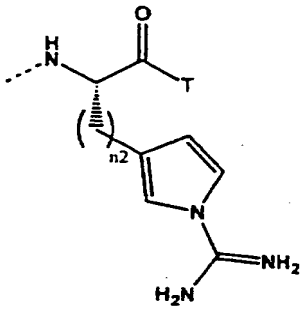


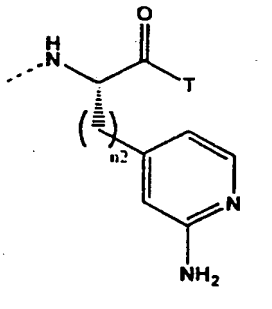


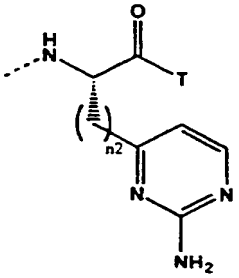


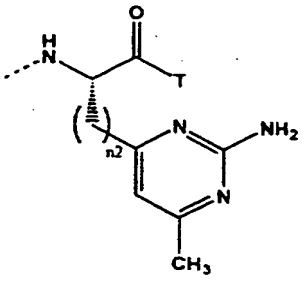


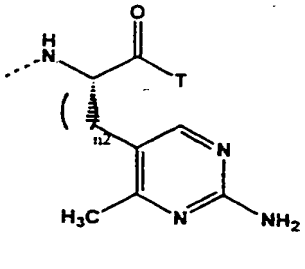


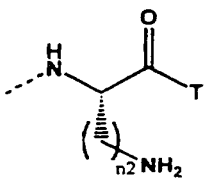


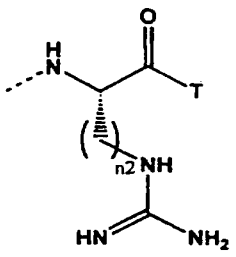


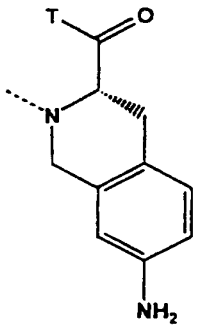


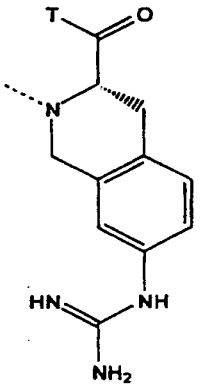


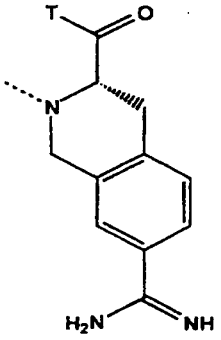


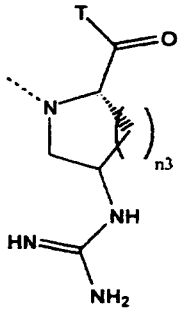


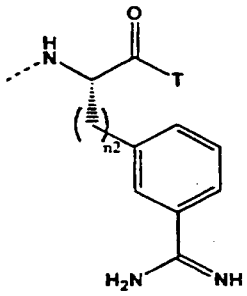


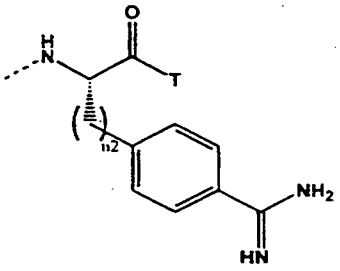


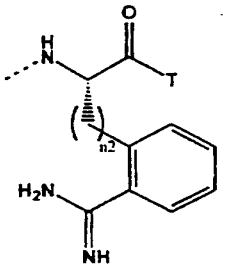


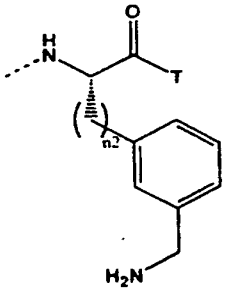


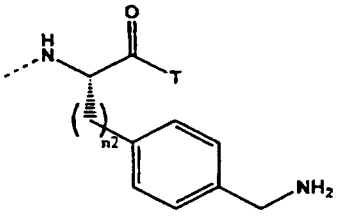


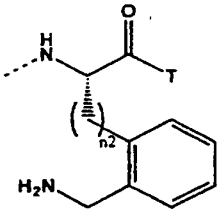


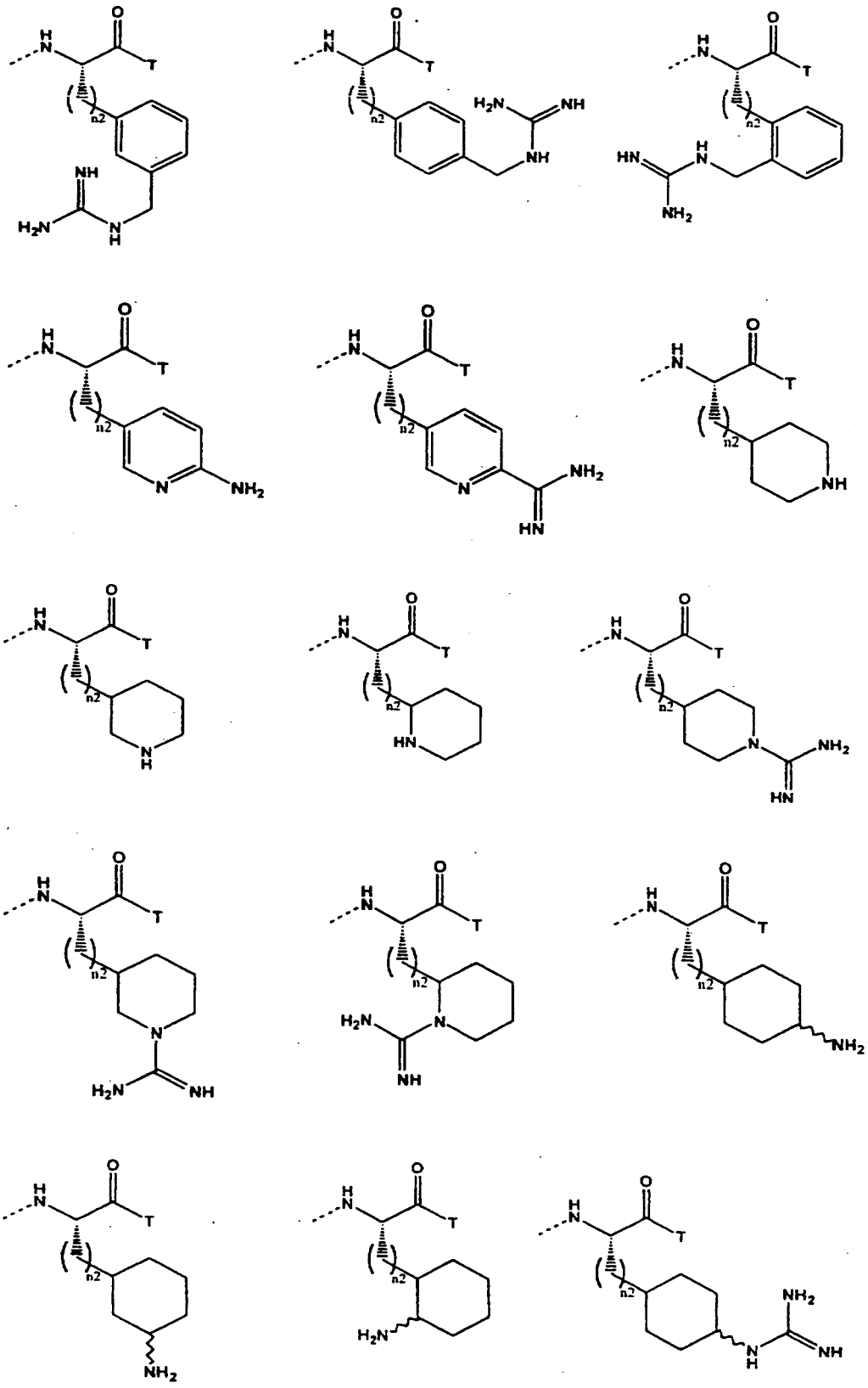












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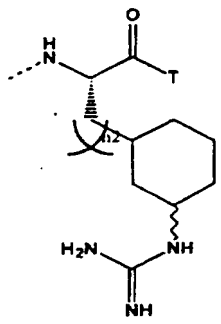
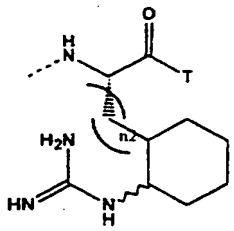
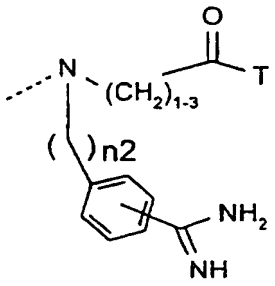
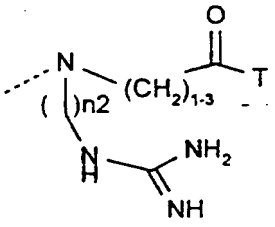
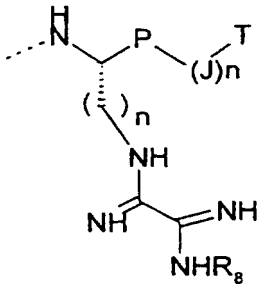
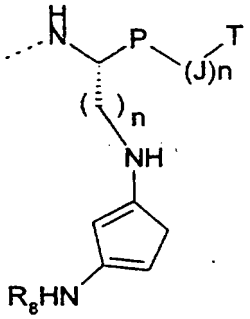
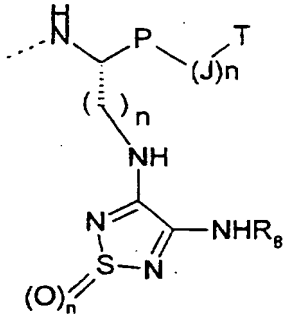
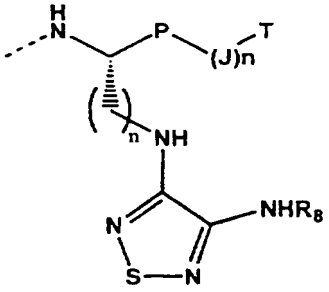
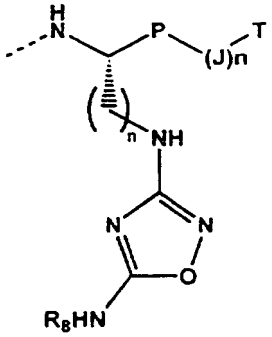
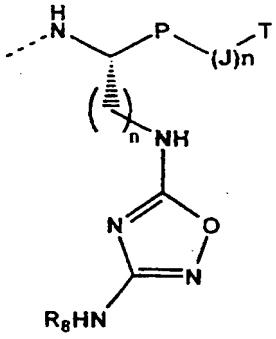
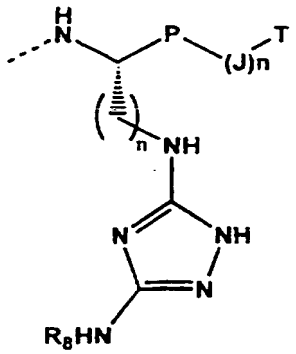
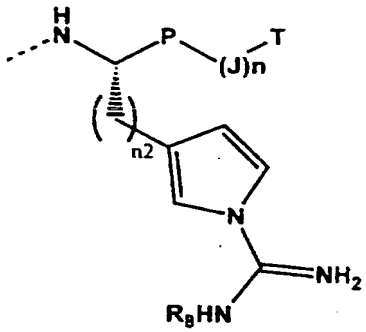





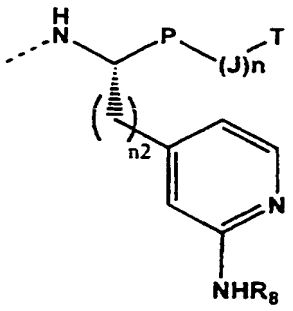
wherein n=1-6, n1=1-2, n2=0-7 and T are as previously defined.

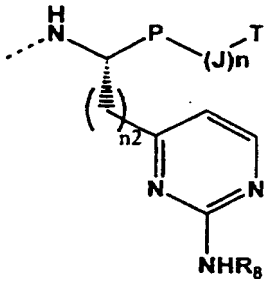
Other amino acid derivatives which R_1 may be selected from include:

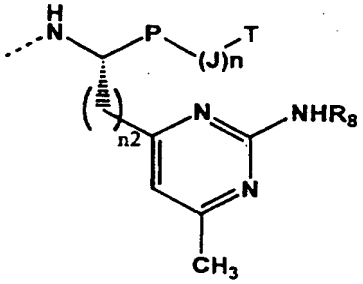







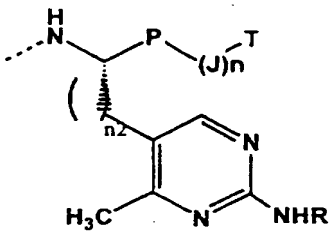


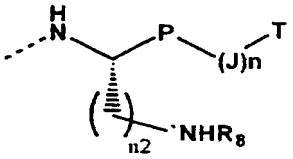


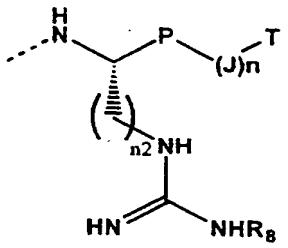


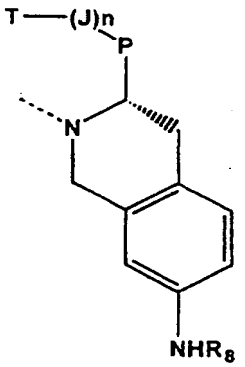


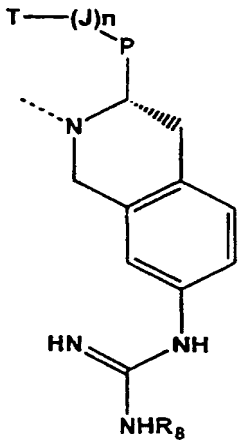


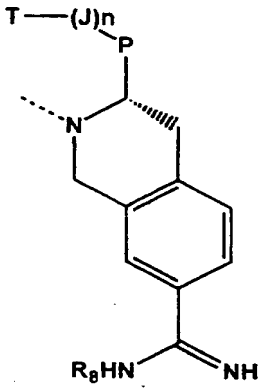


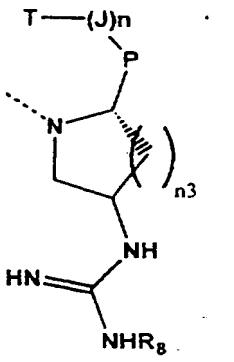


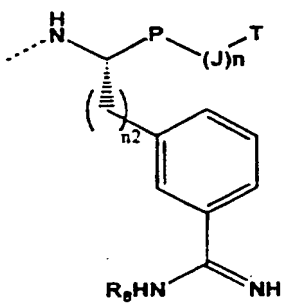
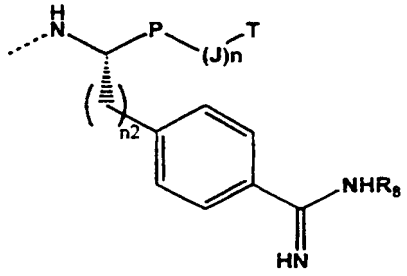
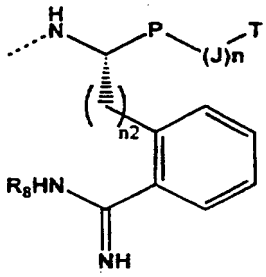
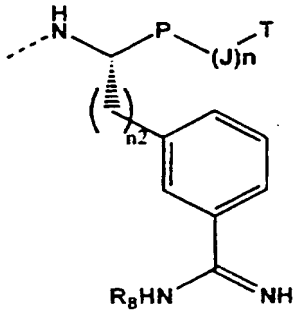
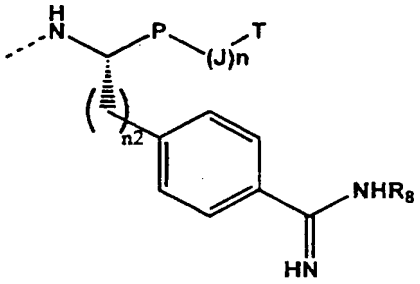
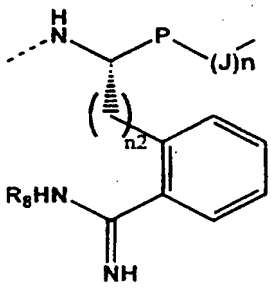
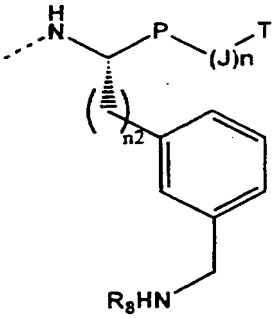
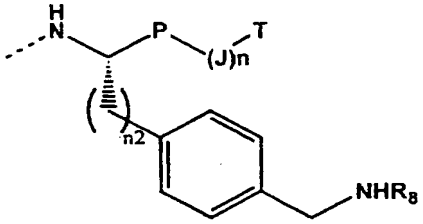
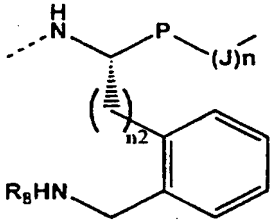
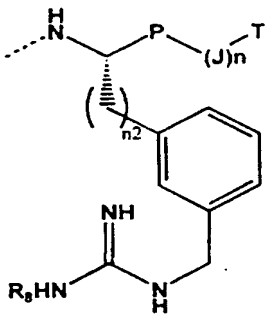
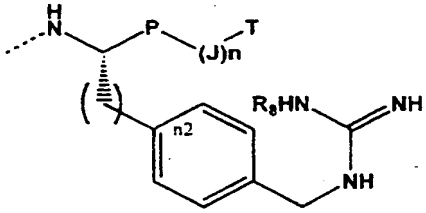
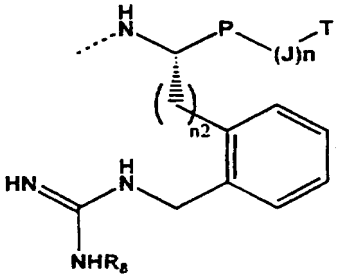
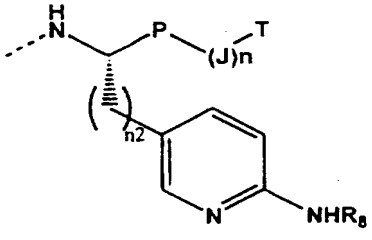
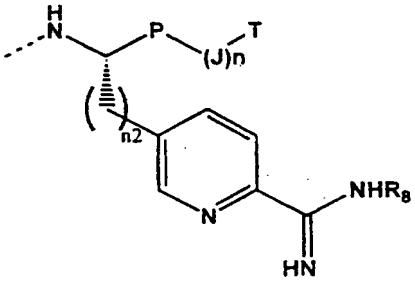
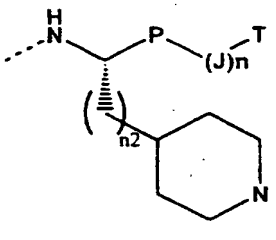


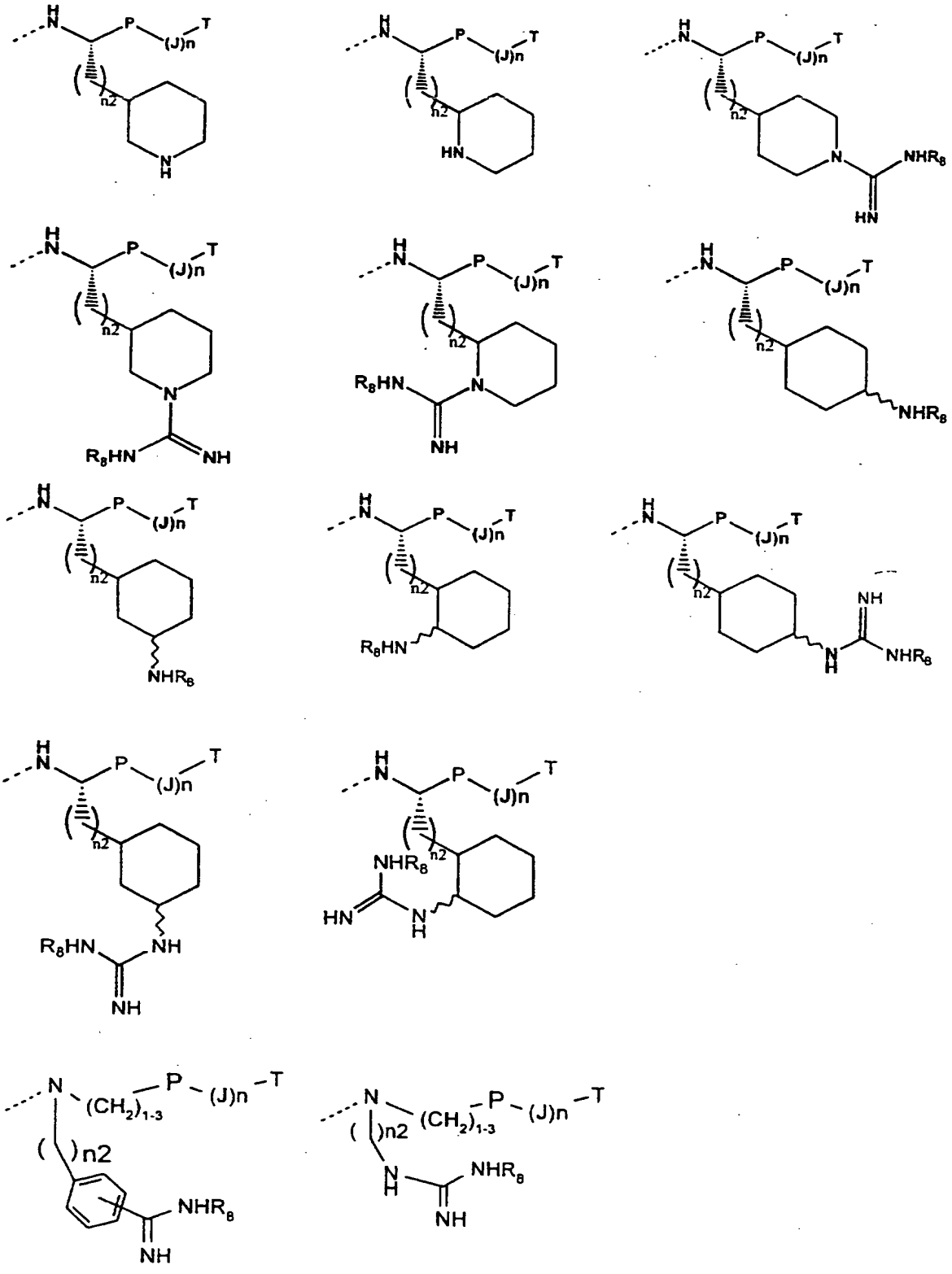


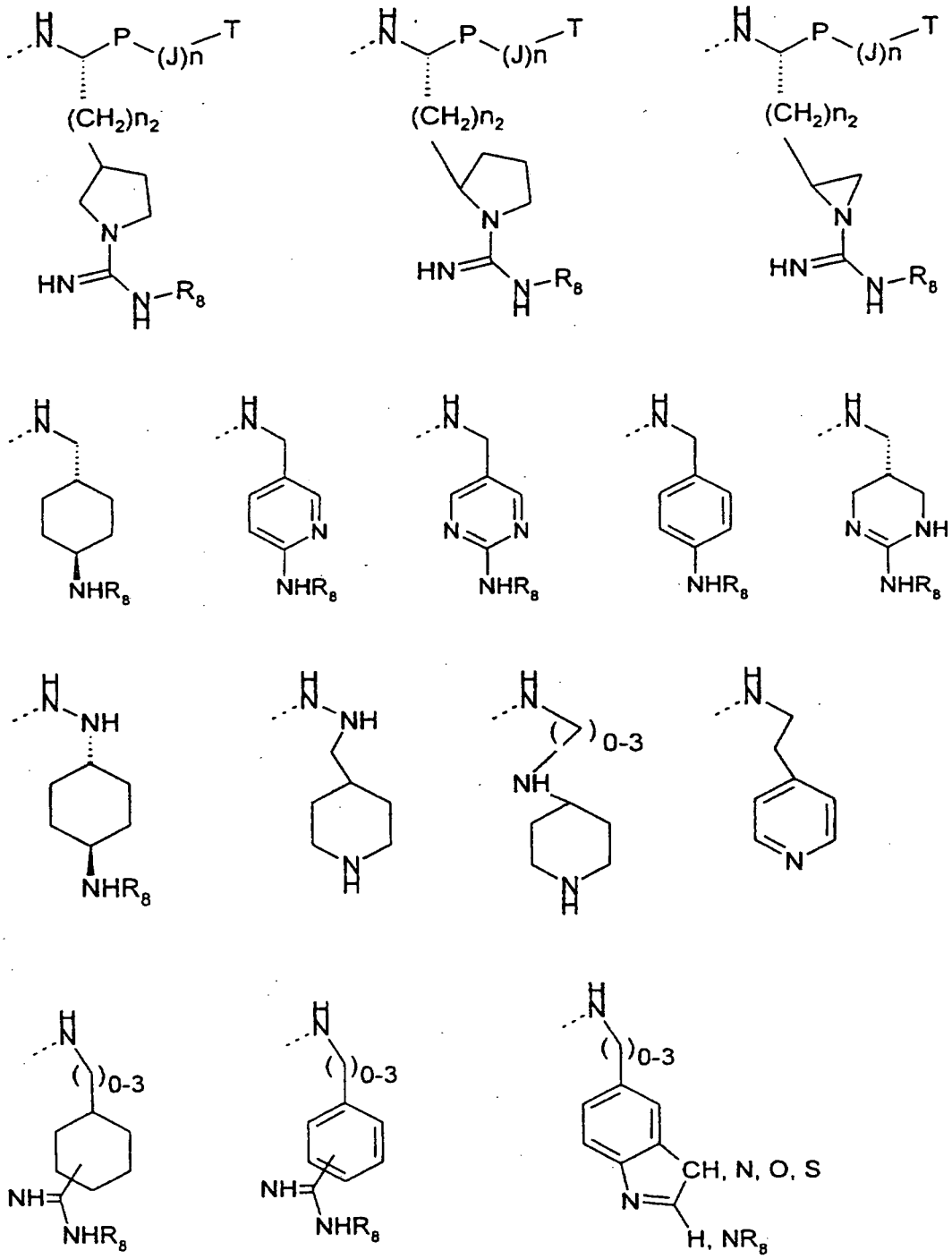






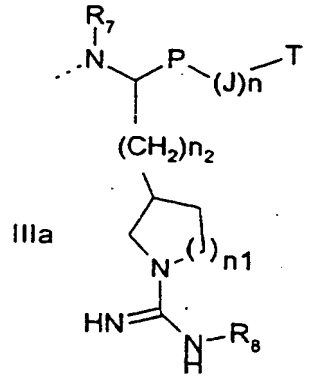


















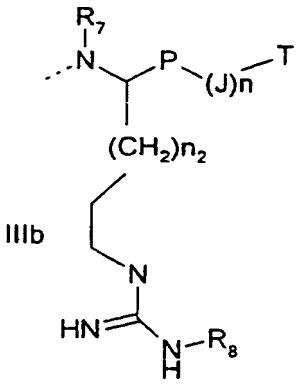


wherein R_8 is H, OH or NH_2; n=1-6, n1=1-2, n2=0-7 and T are as previously defined.

In a preferred embodiment R_1 is a group represented by formula IIIa or IIIb:



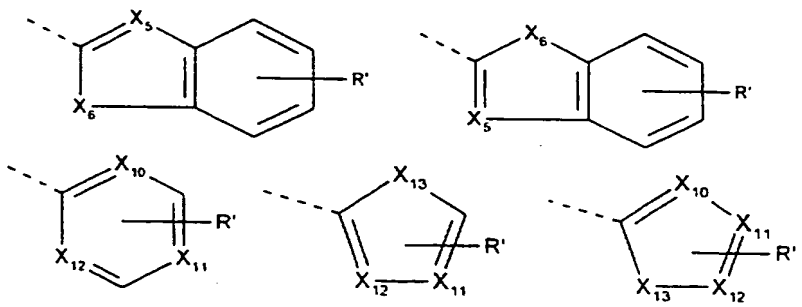
IIIa



IIIb

wherein R_7, R_8, P, J, n, n_2 and T are as previously defined. In a particularly preferred embodiment P is a bond n is 0 and T is H. In another particularly preferred embodiment P is C(O) and n is 0. More preferably n1 is 2. More preferably n2 is 0-3 and most preferably 1. More preferably R_7 is H. More preferably R_8 is H. More preferably R_8 is NH_2. More preferably R_8 is OH.

In a preferred embodiment, T is a peptide of 1 to 4 amino acid residues in length and preferably fibrinogen's A or B chain or fragment or derivative thereof. In another preferred embodiment, T is H while P is a bond and n is 0. In another preferred embodiment, T is selected from H, and amino such as $N(R_9)(R_{10})$, $N(R_9)(OR_{10})$ wherein R_9 and R_{10} are independently H or C_{1-6} alkyl. Alternatively R_9 and R_{10} together with the N from which they depend form a 3-8 member heterocyclic ring (preferably 5 or 6 member) such as piperidine. In another preferred embodiment, T is a heterocycle selected from the group consisting of:



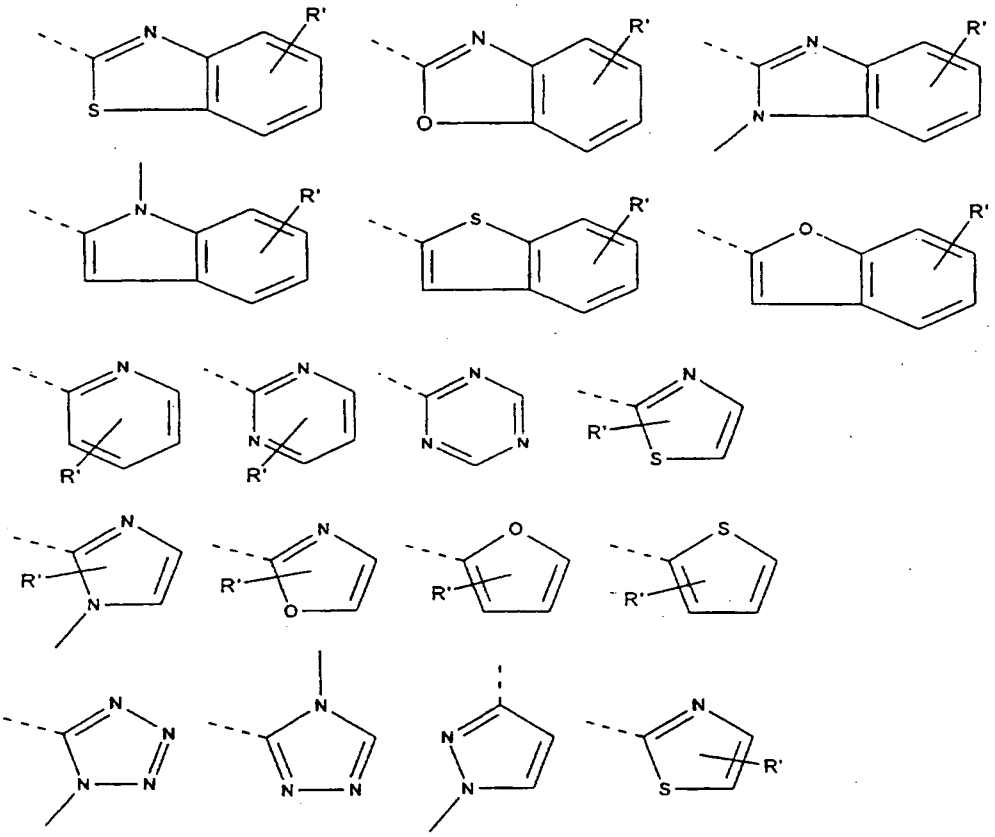
wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from N, and C-X_7 where X_7 is hydrogen, C_{1-4} alkyl, or C_{6-16} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, and CH-X_7;

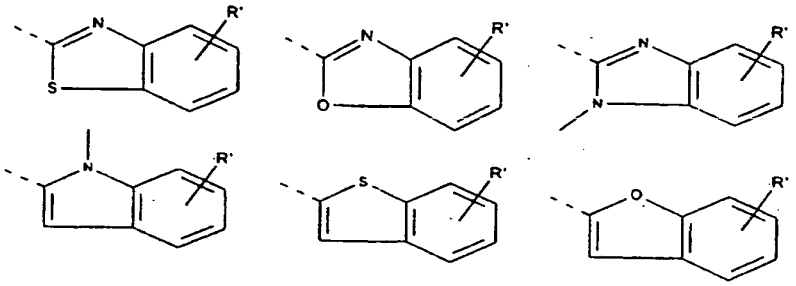
R' is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle. Preparation of heterocycles according to the definition of T is described in PCT application WO 96/19483.

More preferably, T is selected from the group consisting of:



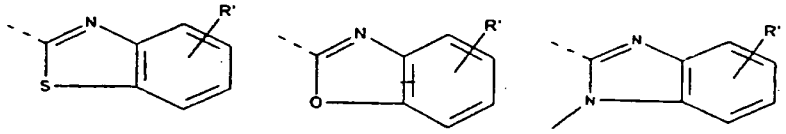
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



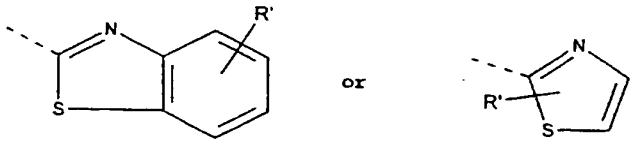
wherein R' is as defined above.

More preferably T is selected from the group consisting of:



wherein R' is as defined above.

Most preferably T is

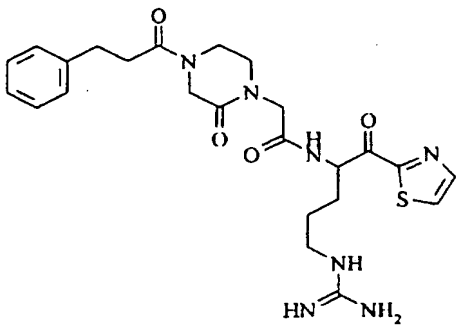


wherein R' is H or C_{1-4} alkyl such as methyl, ethyl, propyl or butyl and most preferably wherein R' is hydrogen,. In another embodiment, T is a 1,2 thiazole optionally substituted with R' and/or is attached to J at the 2, 3, 4 or 5 position of the ring.

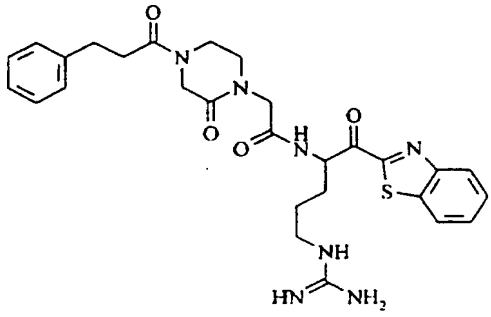
It will be appreciated by those skilled in the art that compounds of formulae (I), depending of the substituents, may contain one or more chiral centers and thus exist in the form of many different isomers, optical isomers (i.e. enantiomers) and mixtures thereof including racemic mixtures. All such isomers, enantiomers and mixtures thereof including racemic mixtures are included within the scope of the invention.

Preferred compounds of the invention include:

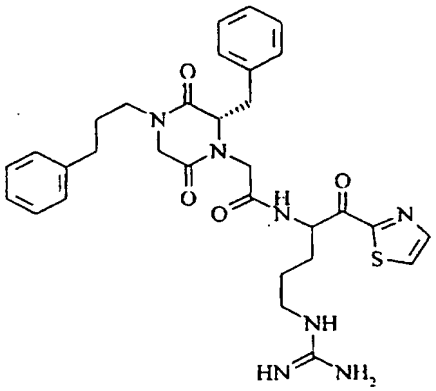
(1) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide



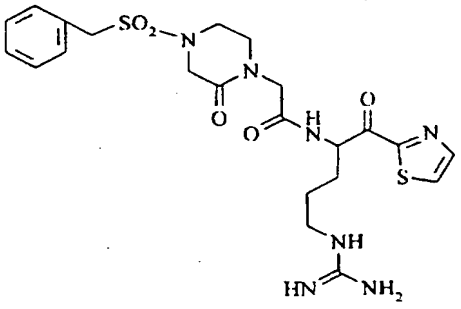
(2) N-[1-(benzothiazole-2 carbonyl)-4-guanidino-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide



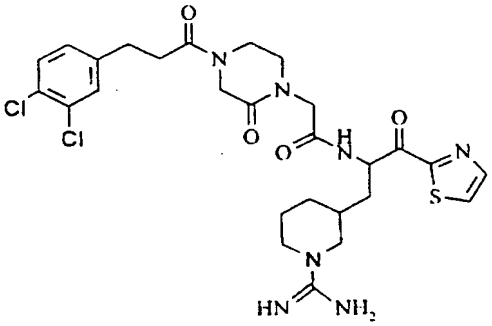
(3) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide



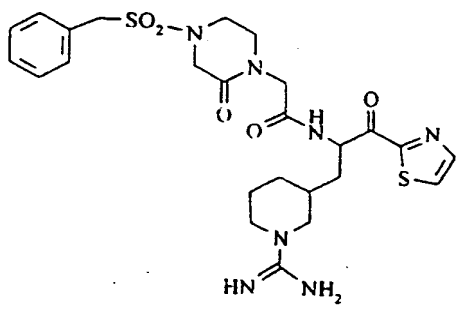
(4) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)acetamide



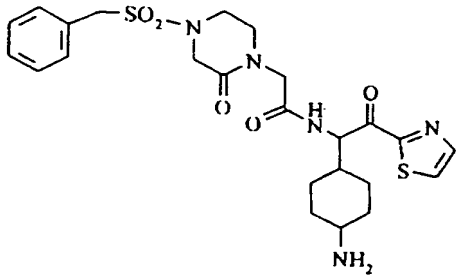
(5) N-[1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-{4-[(3,4-dichloro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-acetamide



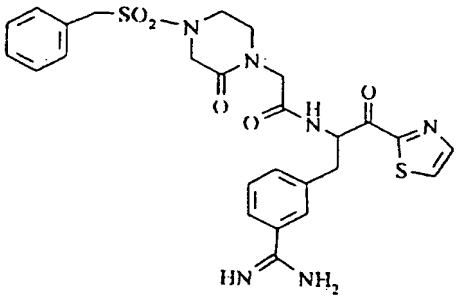
(6) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide



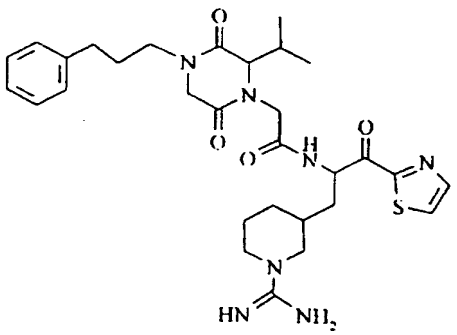
(7) N-[1-(4-amino-cyclohexyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl}-acetamide



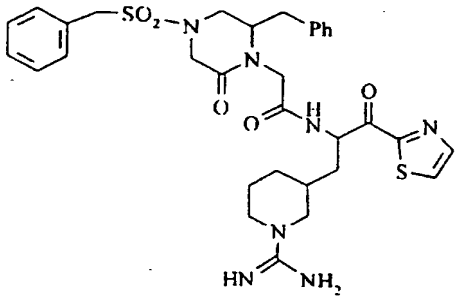
(8) N-[1-(3-carbamimidoyl-benzyl)-2-oxo-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide



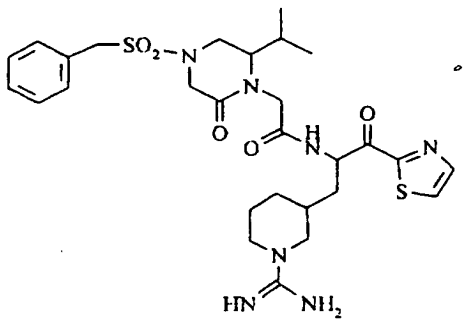
(9) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-isopropyl-6-oxo-4-(3-phenyl-propyl)-piperazin-1-yl}-acetamide



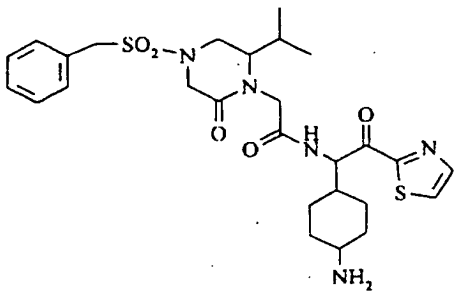
(10) 2-(2-benzyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-ylethyl]acetamide



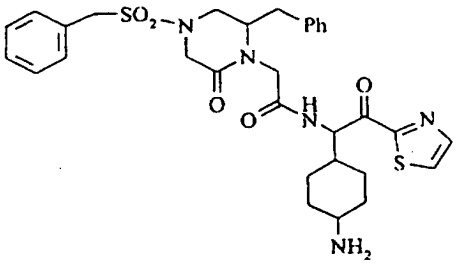
(11) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-isopropyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide



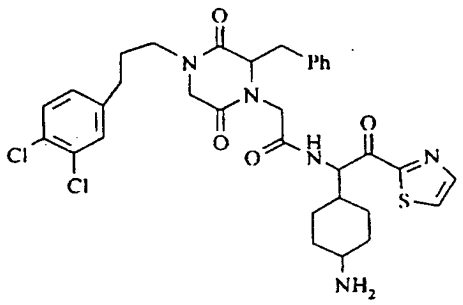
(12) N-[1-(4-aminocyclohexyl)-2-thiazol-2-ylethyl]-2-(2-isopropyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide



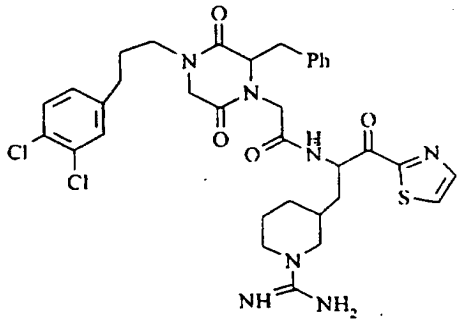
(13) N-[1-(4-aminocyclohexyl)-2-oxo-2-thiazol-2-ylethyl]-2-(2-benzyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide



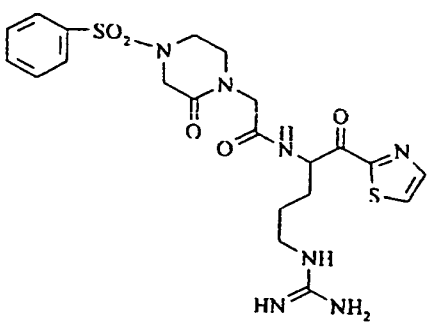
(14) N-[1-(4-aminocyclohexyl)-2-oxo-2-thiazol-2-ylethyl]-2-{2-benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-acetamide



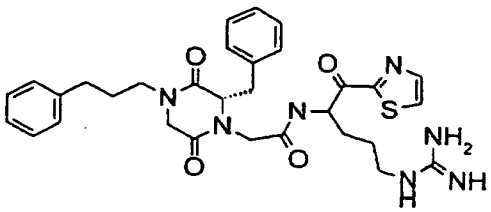
(15) 2-{2-benzyl-4-[3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-ylethyl]-acetamide



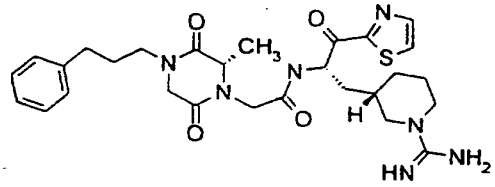
(16) 2-(4-benzenesulfonyl-2-oxo-piperazin-1-yl)-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide



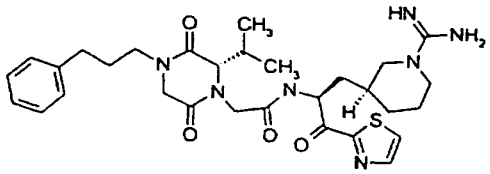
(20) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide



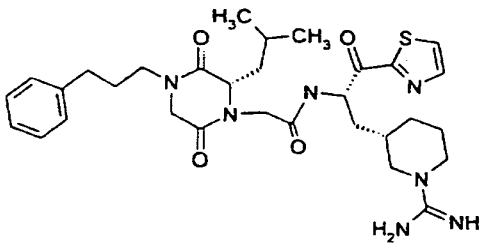
(21) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-methyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



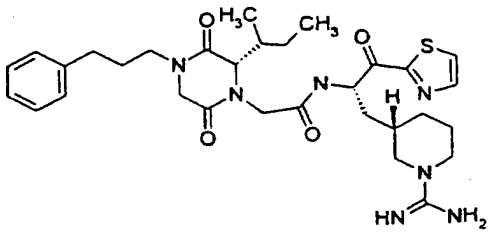
(22) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-isopropyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



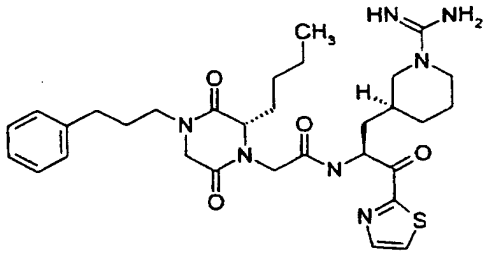
(23) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-isobutyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



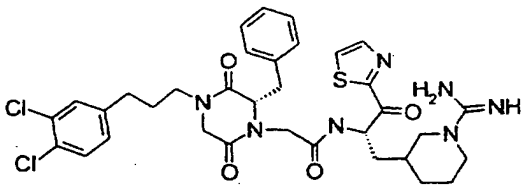
(24) 2-[2-sec-Butyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide



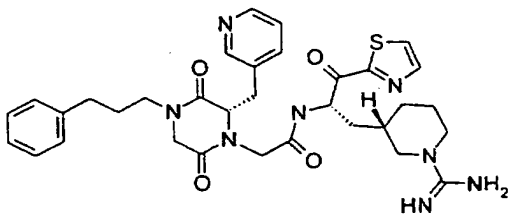
(25) 2-[2-Butyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



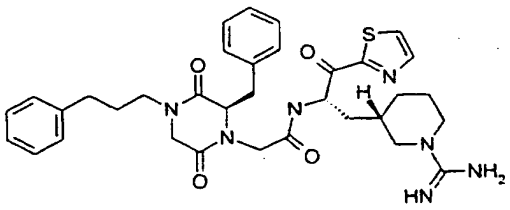
(26) 2-{2-Benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



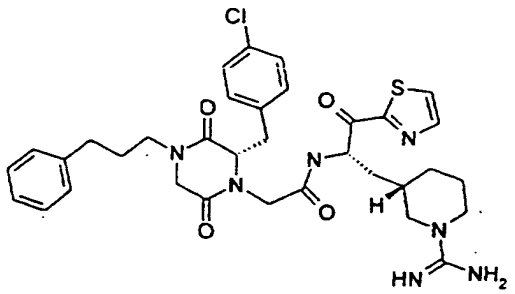
(27) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[3,6-dioxo-4-(3-phenyl-propyl)-2-pyridin-3-ylmethyl-piperazin-1-yl]-acetamide



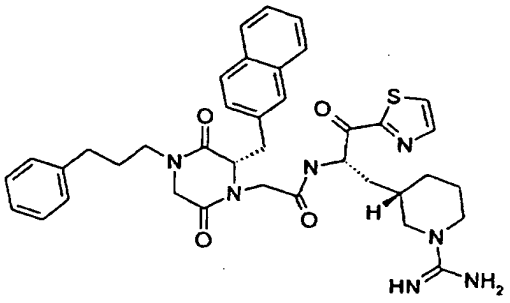
(28) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



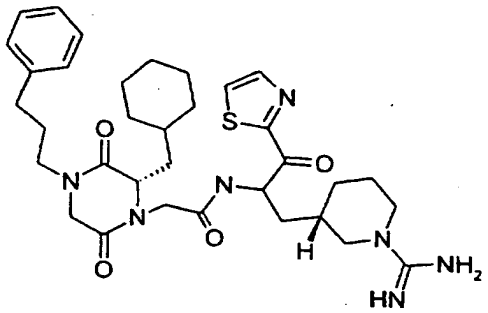
(29) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[3-(4-chloro-benzyl)-2,5-dioxo-1-(3-phenyl-propyl)-piperidin-4-yl]-acetamide



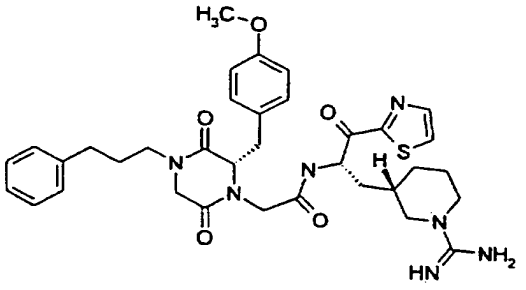
(30) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



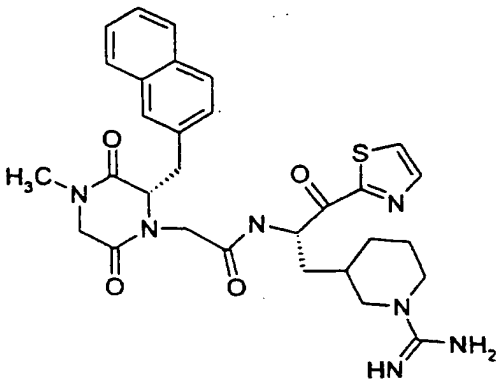
(31) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-cyclohexylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



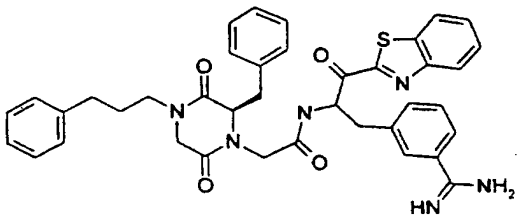
(32) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(4-methoxy-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



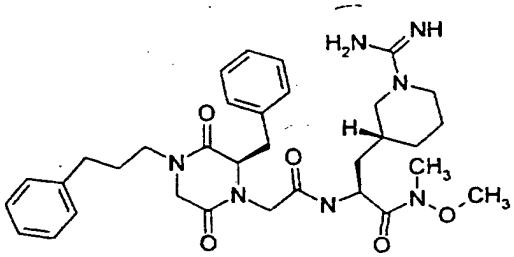
(33) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide



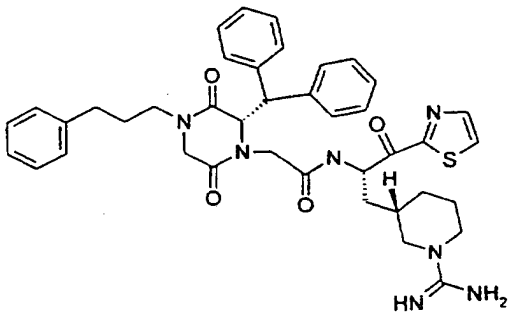
(34) N-[2-Benzothiazol-2-yl-1-(3-carbamimidoyl-benzyl)-2-oxo-ethyl]-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



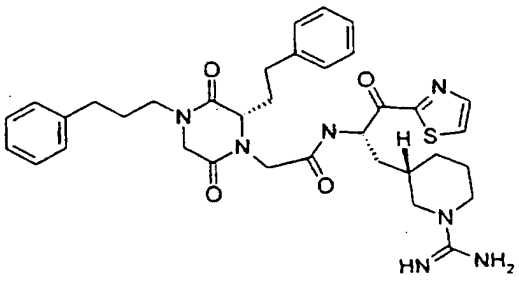
(35) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-methoxy-N-methyl-propionamide



(36) 2-[2-Benzhydryl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide

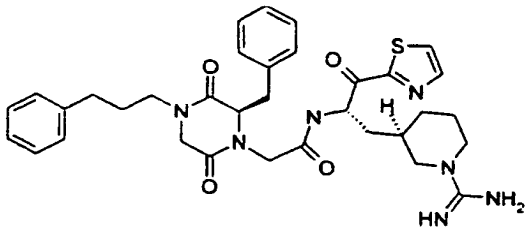


(37) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[3,6-dioxo-2-phenethyl-4-(3-phenyl-propyl)-piperazin-1-yl]-

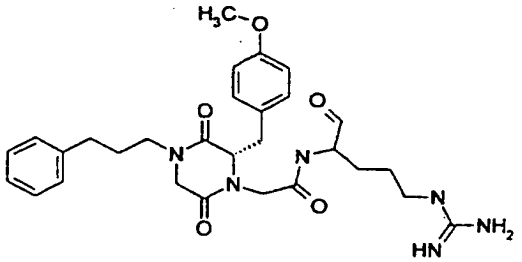


acetamide

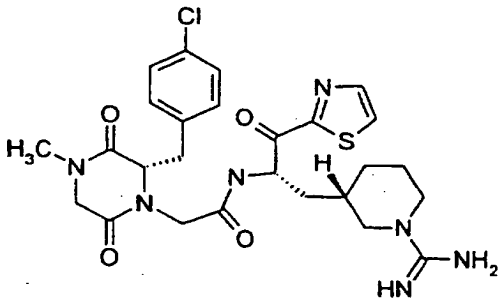
(38) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



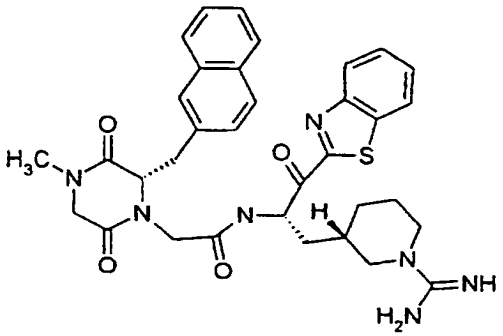
(39) N-(1-Formyl-4-guanidino-butyl)-2-[2-(4-methoxy-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



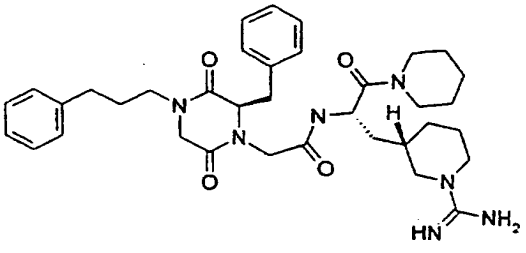
(40) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(4-chloro-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide



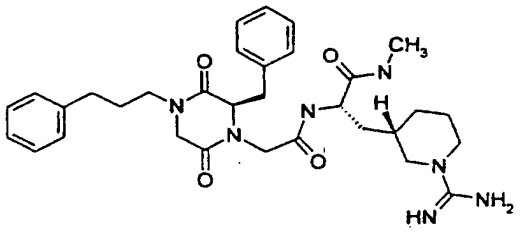
(41) N-[2-Benzothiazol-2-yl-1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide



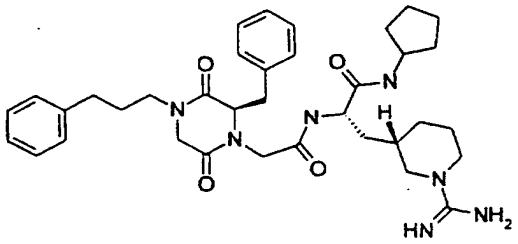
(42) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-acetamide



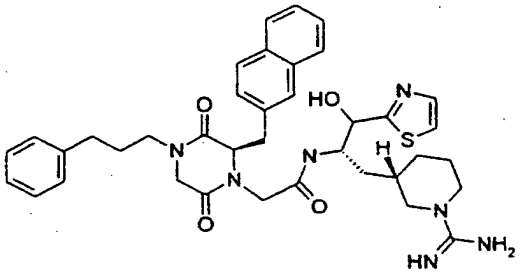
(43) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-methyl-propionamide



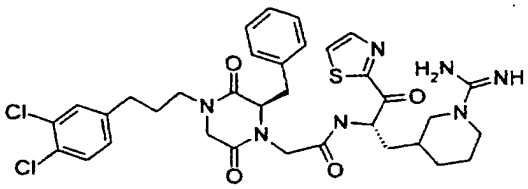
(44) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-cyclopentyl-propionamide



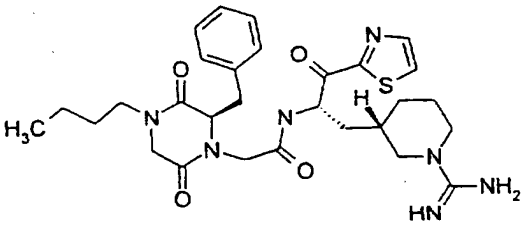
(45) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(hydroxy-thiazol-2-yl-methyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



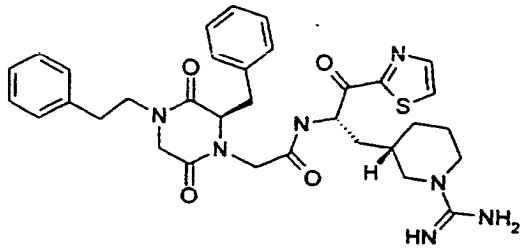
(46) 2-{2-Benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



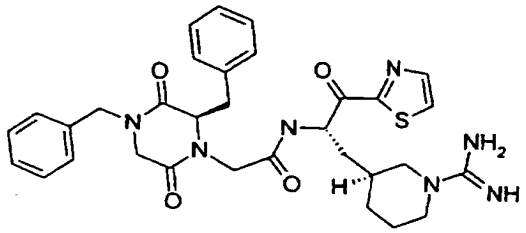
(47) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



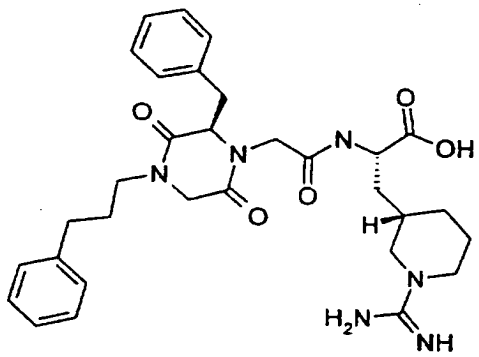
(48) 2-(2-Benzyl-3,6-dioxo-4-phenethyl-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



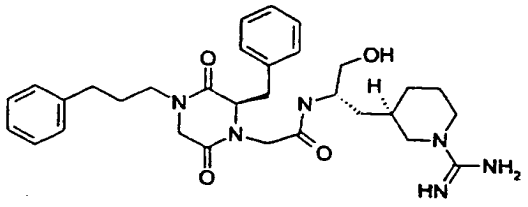
(49) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(2,4-dibenzyl-3,6-dioxo-piperazin-1-yl)-acetamide



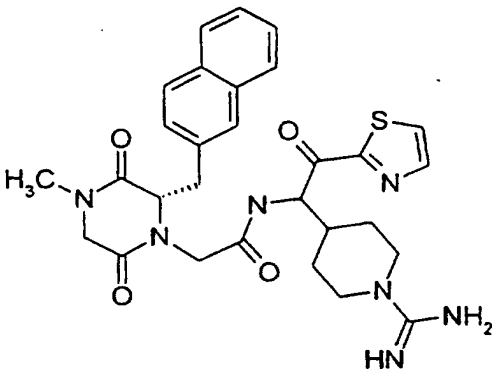
(50) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(2,4-dibenzyl-3,6-dioxo-piperazin-1-yl)-acetamide



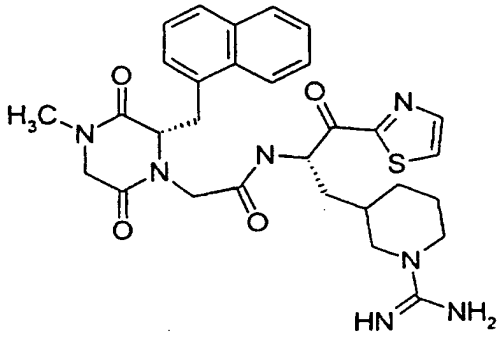
(51) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-hydroxymethyl-ethyl]-acetamide



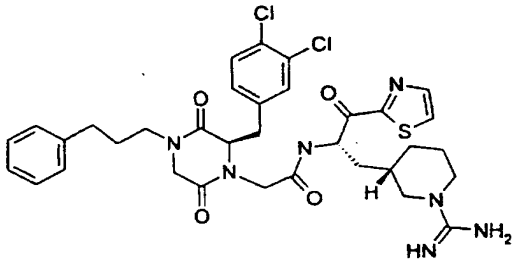
(52) N-[1-(1-Carbamimidoyl-piperidin-4-yl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide



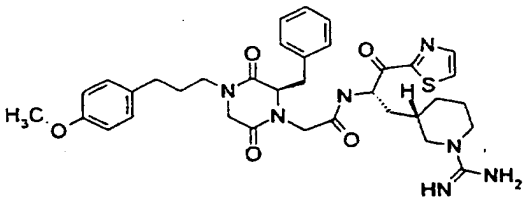
(53) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(4-methyl-2-naphthalen-1-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide



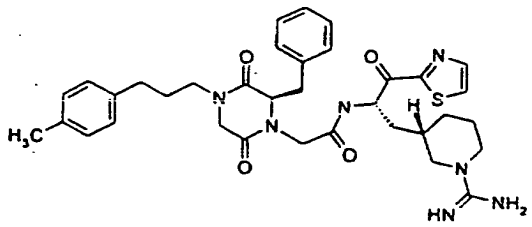
(54) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



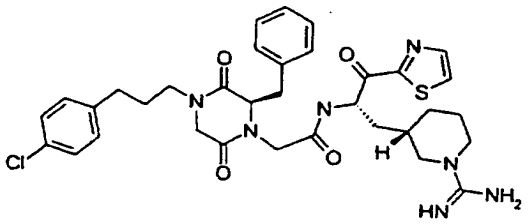
(55) 2-(2-Benzyl-4-[3-(4-methoxy-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



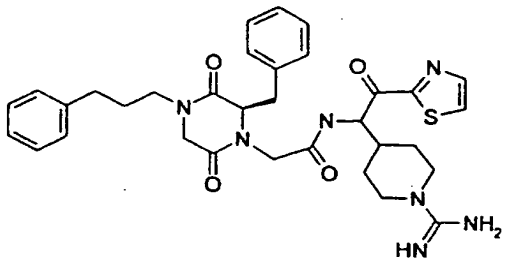
(56) 2-[2-Benzyl-3,6-dioxo-4-(3-p-tolyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



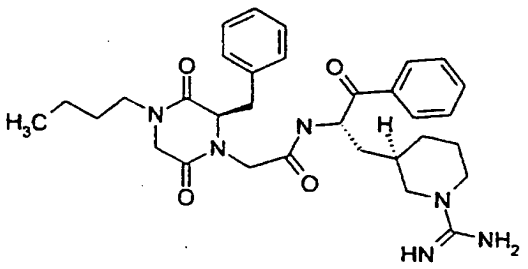
(57) 2-{2-Benzyl-4-[3-(4-chloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



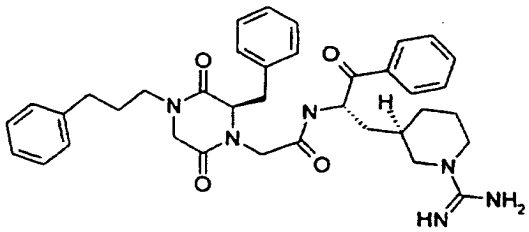
(58) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-4-yl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide



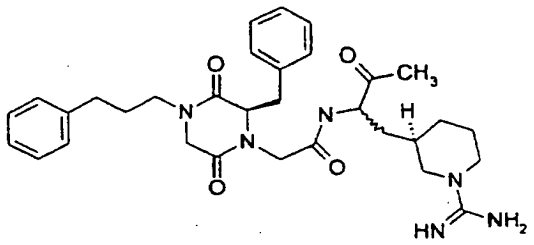
(59) N-[1-Benzoyl-2-(1-carbamimidoyl-piperidin-3-yl)-ethyl]-2-(2-benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-acetamide



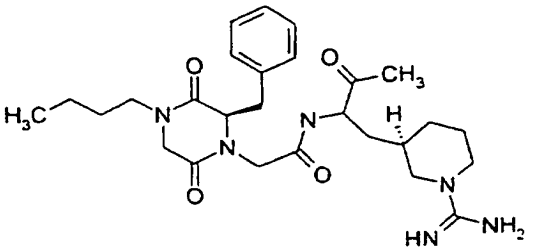
(60) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-phenyl-ethyl]-acetamide



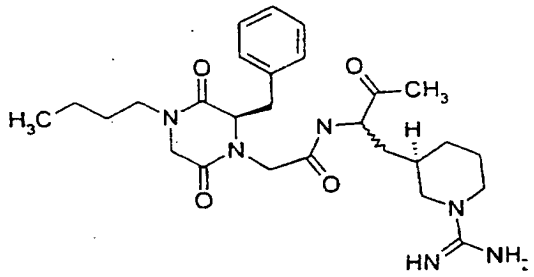
(61) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide



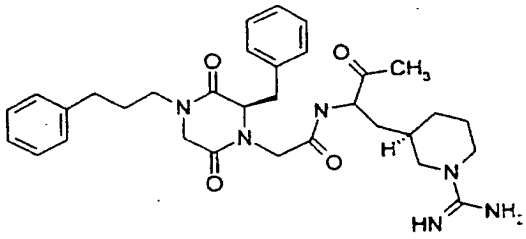
(62) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide



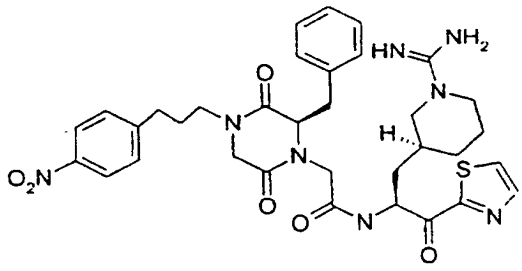
(63) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide



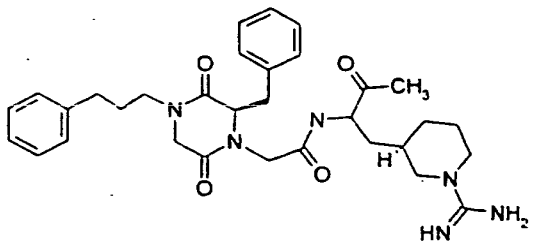
(64) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide



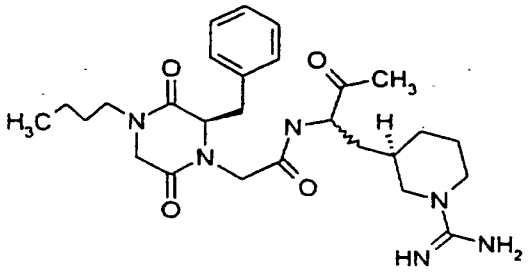
(65) 2-{2-Benzyl-4-[3-(4-nitro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



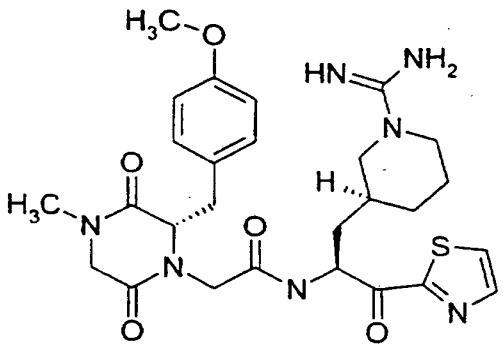
(66) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide



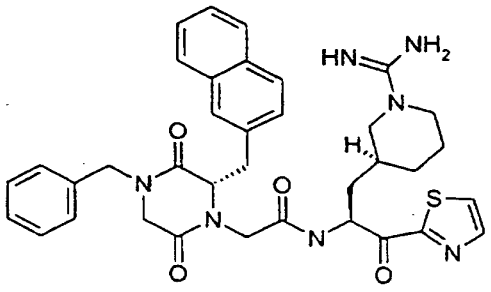
(67) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide



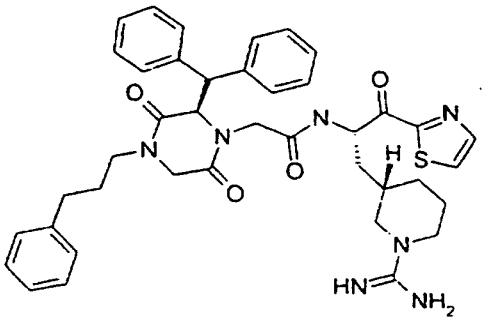
(68) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(4-methoxy-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide



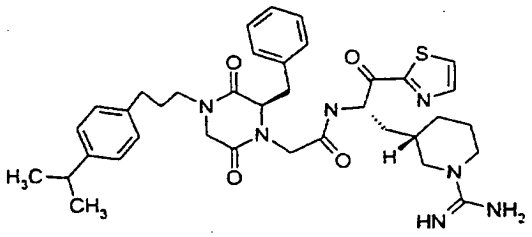
(69) 2-(4-Benzyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



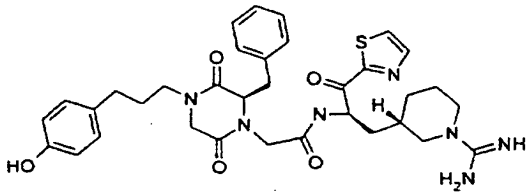
(70) 2-[2-Benzhydryl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



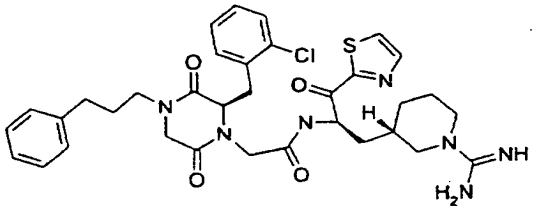
(71) 2-{2-Benzyl-4-[3-(4-isopropyl-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



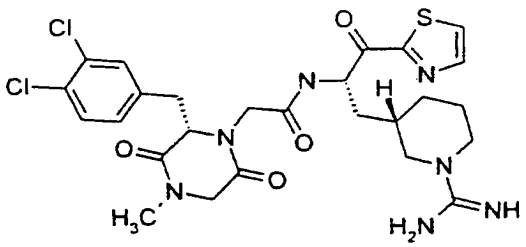
(72) 2-{2-Benzyl-4-[3-(4-hydroxy-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



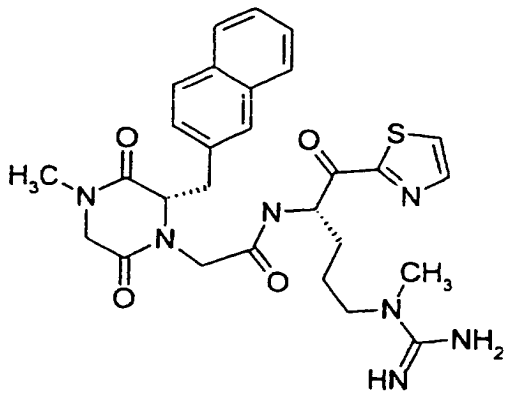
(73) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



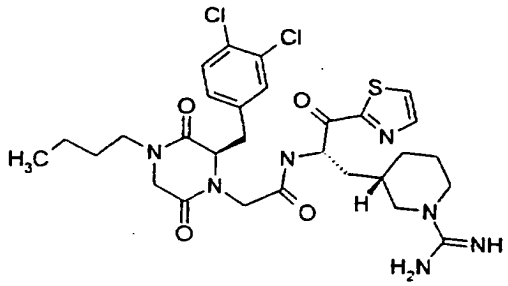
(74) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide



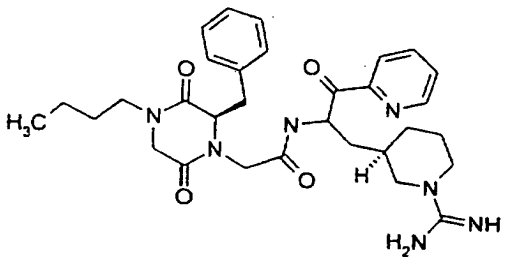
(75) N-[4-(N-Methyl-guanidino)-1-(thiazole-2-carbonyl)-butyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide



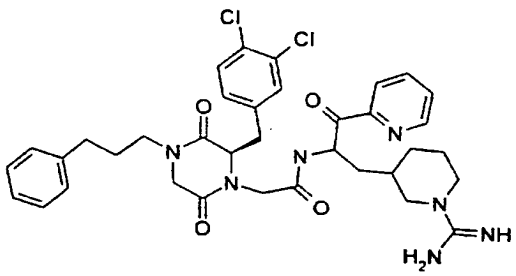
(76) 2-[4-Butyl-2-(3,4-dichloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



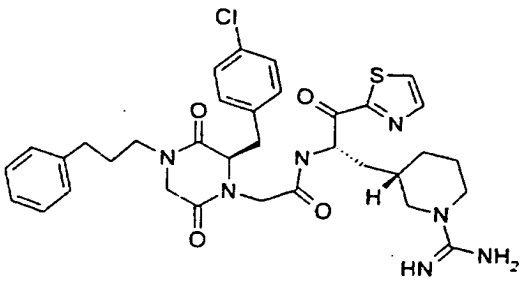
(77) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(pyridine-2-carbonyl)-ethyl]-acetamide



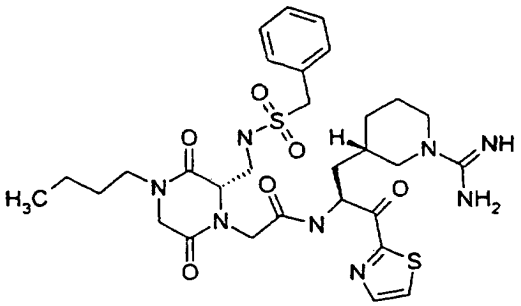
(78) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(pyridine-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



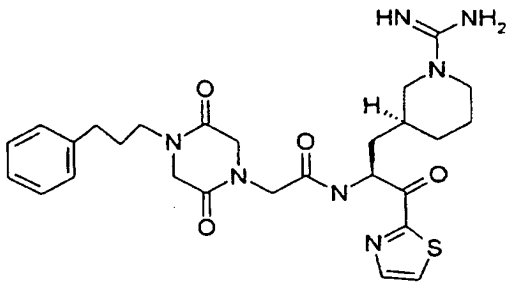
(79) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(4-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



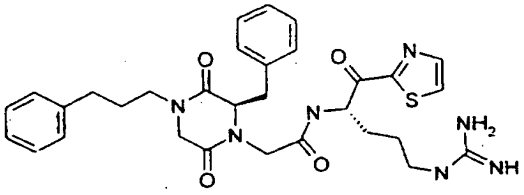
(80) 2-[4-Butyl-3,6-dioxo-2-(phenylmethanesulfonylamino-methyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



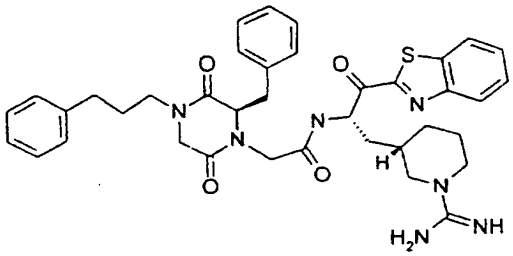
(81) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2,5-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



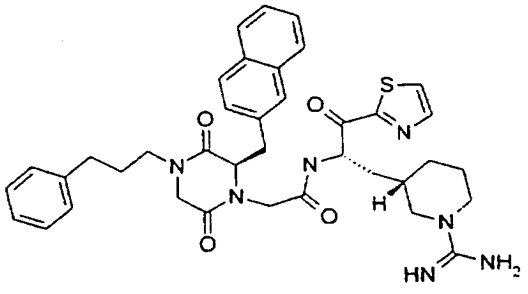
(82) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidine-1-(thiazole-2-carbonyl)-butyl]-acetamide



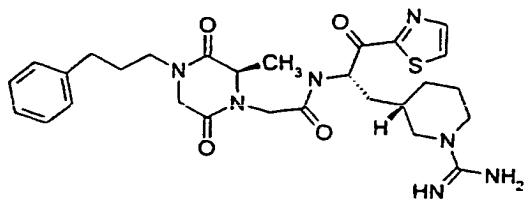
(83) N-[2-benzothiazol-2-yl-1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-ethyl]-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



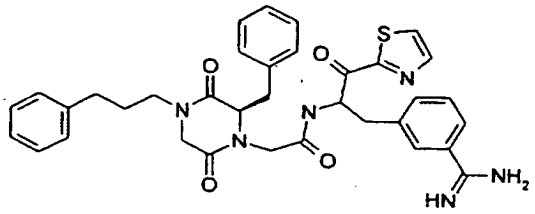
(84) N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



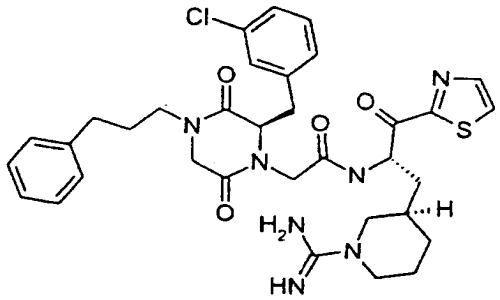
(85) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-thiazol-2-yl-ethyl]-2-[2-methyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



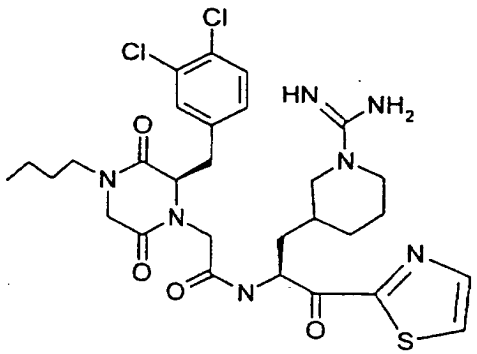
(86) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(3-carbamimidoyl-phenyl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide



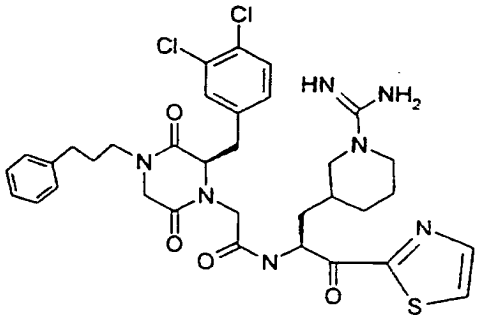
(87) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(3-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



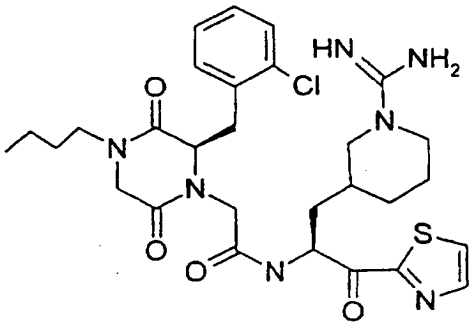
(88) 2[4-butyl-2-(3,4-dichloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2yl-ethyl]acetamide



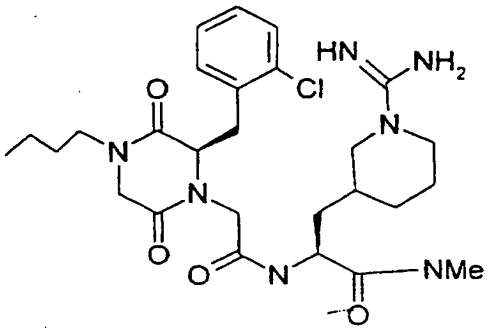
(89) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperzin-1-yl]-acetamide



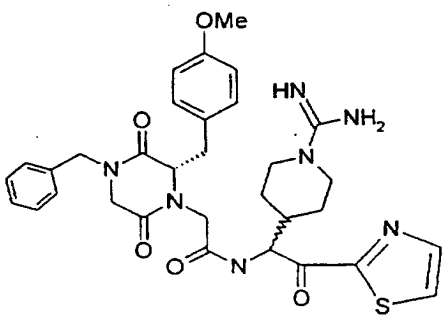
(90) 2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide



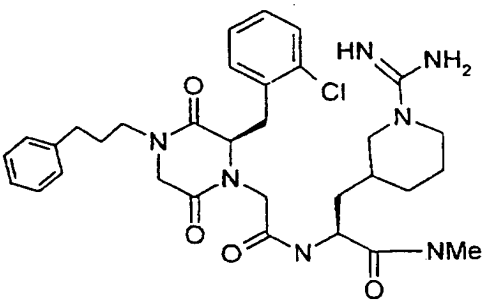
(91) 2{2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]acetylamino}-3-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide



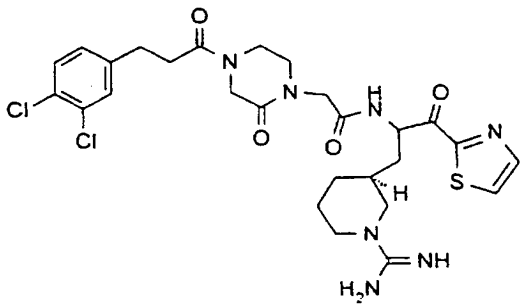
(92) 2-[4-benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide



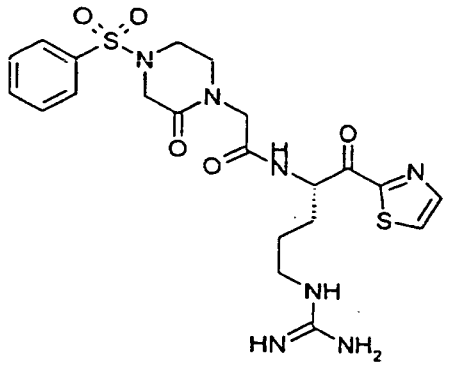
(93) 3-(1-carbamimidoyl-piperidine-3-yl)-2-[2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino]-N-methyl-propionamide



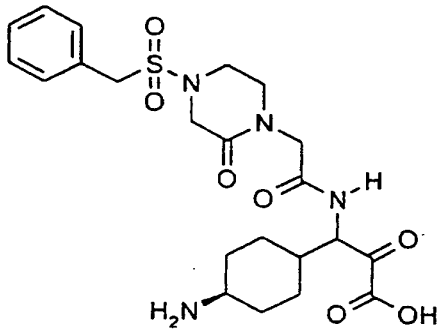
(94) (3S)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-{4-[3-(3,4-dichloro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-acetamide



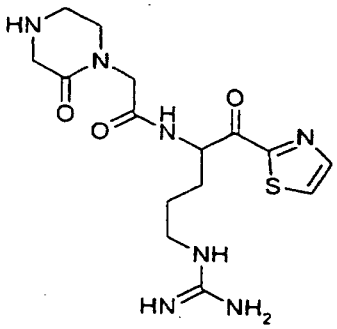
(95) 2-(4-Benzenesulfonyl-2-oxo piperazin-1-yl)-*N*-[1-(benzothiazole-2-carbonyl) guanidino-butyl]-acetamide



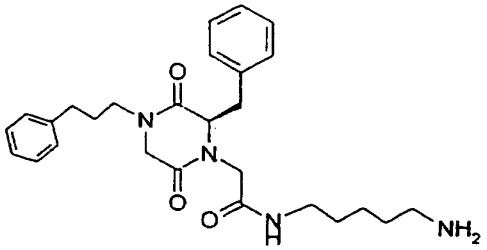
(96) 4-{2-Carboxy-2-oxo-1-[2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl)-acetylamino]-ethyl}-cyclohexylamine



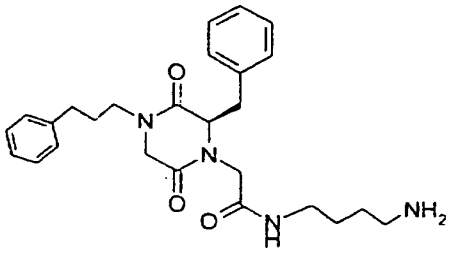
(97) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-piperazin-1-yl)-acetamide



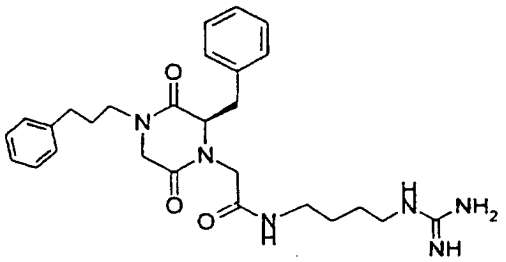
(98) 5-[(2R)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazinan-1-ylmethyl-carboxamido]pentylamine



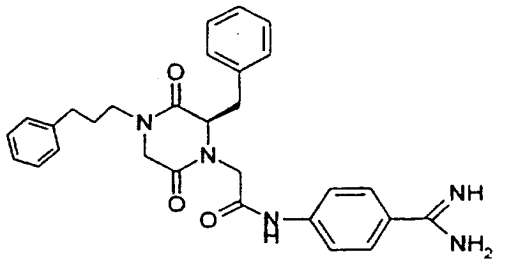
(99) 4-(2S)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazan-1-ylmethyl-carboxamido]butylamine



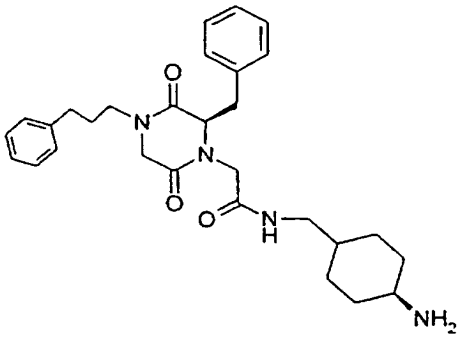
(100) 4-[(2R)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazinan-1-ylmethyl-carboxamido]guanidinobutane



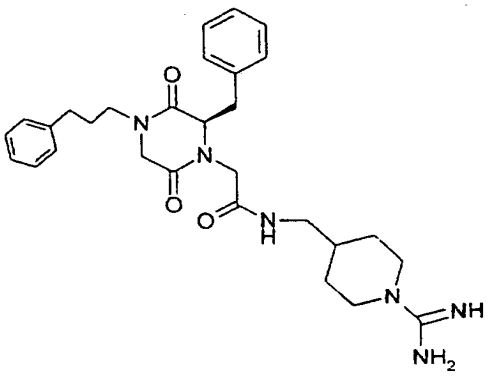
(101) N-(4-carbamimidoyl-phenyl)-2-[2-cyclohexa-2,4-dienylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]acetamide



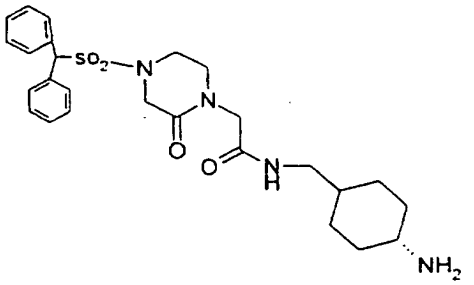
(102) N-(4-amino-cyclohexyl-methyl)-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide



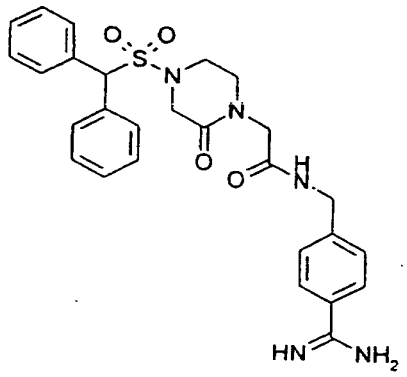
(103) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-(1-carbozmimdoyl-piperidin-4-ylmethyl)-acetamide



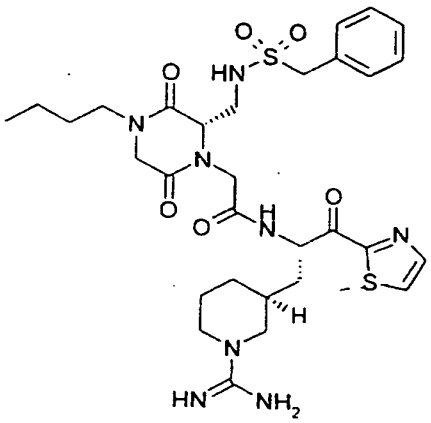
(104) *N*-(4-Amino-cyclohexyl-methyl)-2-[4-(diphenyl-methanesulfonyl)-2-oxo-piperazin-1-yl]-acetamide



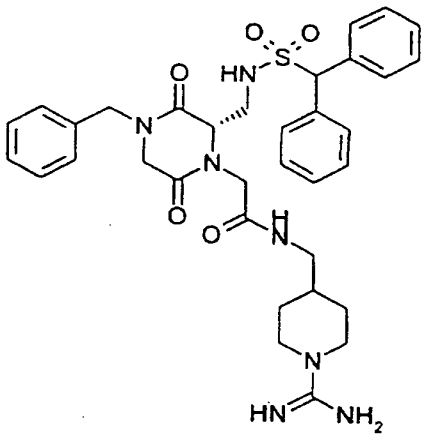
(105) *N*-(4-Carbamimidoyl-benzyl)-2-[4-(diphenyl-methanesulfonyl)-2-oxo-piperazin-1-yl]-acetamide



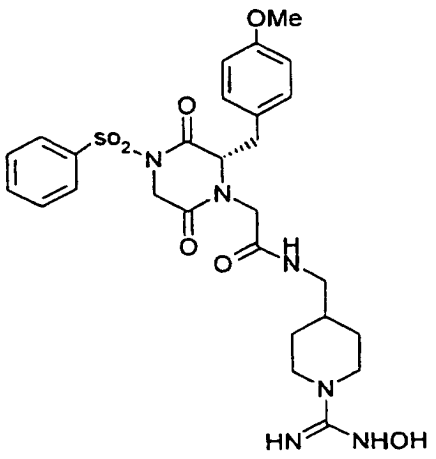
(106) 2-[4-Butyl-3,6-dioxo-2-(phenylmethanesulfonylamino-methyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide



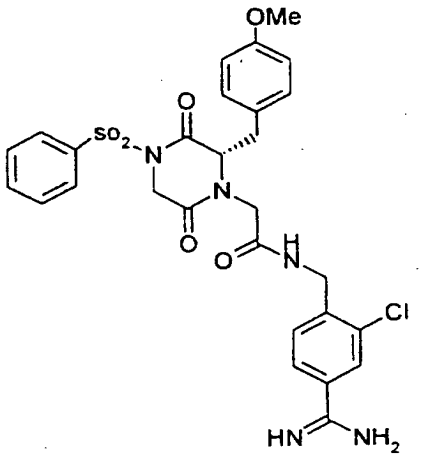
(107) 2-{4-Benzyl-2-[(diphenyl-methanesulfonylamino)-methyl]-3,6-dioxo-piperazin-1-yl}-N-(1-carbamimidoyl-piperidin-4-ylmethyl)-acetamide



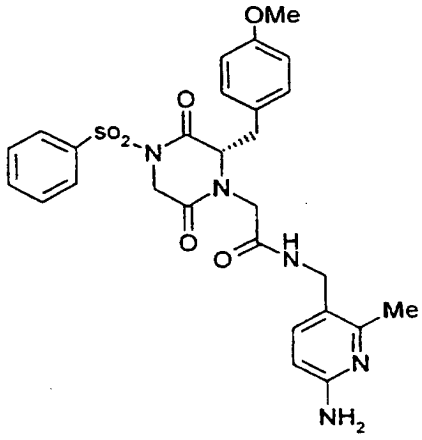
(108) 2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-N-(1-carbamimidoyl-piperidin-4-ylmethyl)-acetamide



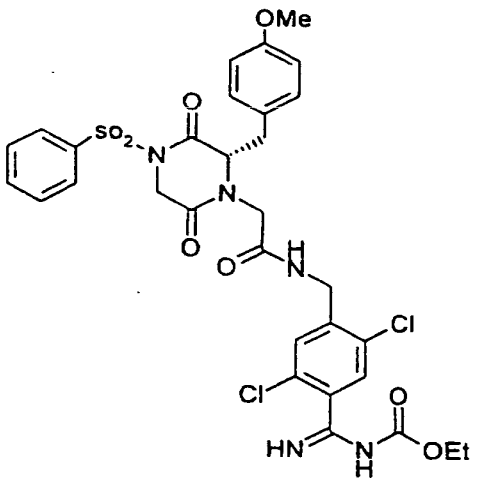
(109) 2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-*N*-(4-carbamimidoyl-2-chloro-benzyl)-acetamide



(110) *N*-(6-Amino-2-chloro-pyridin-3-ylmethyl)-2-[4-benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-acetamide

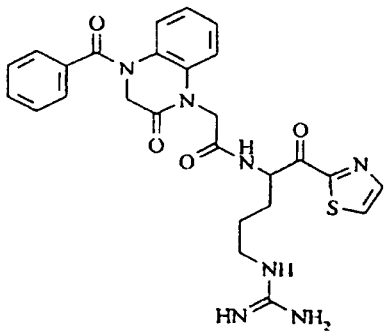


(111) {[4-({2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-acetylamino}-methyl)-2,5-dichloro-phenyl]-imino-methyl}-carbamic acid ethyl ester.

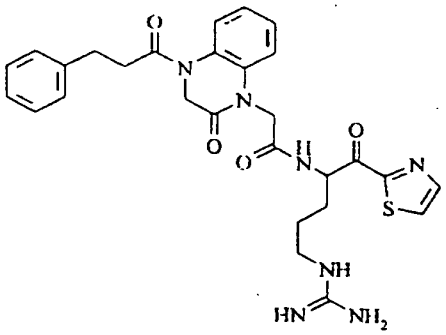


Other preferred compounds of the invention, wherein R_3 and R_4 from substituent Y together form a 5 or 6 member saturated or unsaturated carbocyclic ring, include:

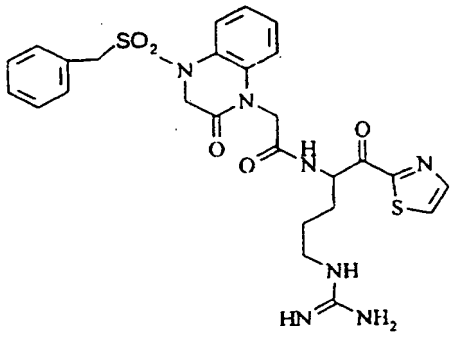
(17) 2-(4-benzoyl-2-oxo-3,4-dihydro-2H-quinoxalin-1-yl)-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide



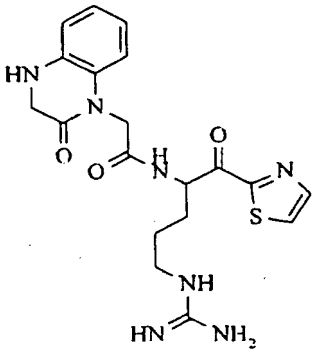
(18) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-3,4-dihydro-2H-quinoxalin-1-yl]-acetamide



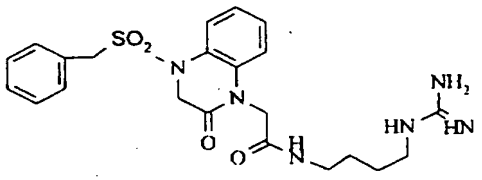
(19) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihyero-2H-quinoxalin-1-yl)acetamide



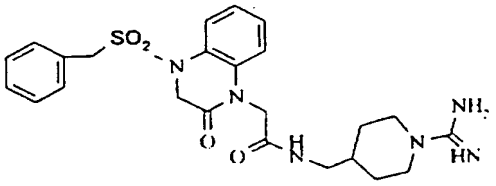
(112) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-3,4-dihydro-2H-quinoxalin-1-yl)-acetamide



(113) *N*-(4-Guanidino-butyl)-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihydro-2*H*-quinoxalin-1-yl)-acetamide



(114) *N*-(1-Carbamimidoyl-piperidin-4-ylmethyl)-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihydro-2*H*-quinoxalin-1-yl)-acetamide



Particularly preferred compounds of the present invention include:

(3) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide;

(14) N-[1-(4-aminocyclohexyl)-2-oxo-2-thiazol-2-ylethyl]-2-{2-benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-acetamide;

(15) 2-{2-benzyl-4-[3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[1-(1-carbamimidoyl-piperidin-3-

ylmethyl)-2-oxo-2-thiazol-2-ylethyl]-acetamide;

(28) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(43) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-methyl-propionamide;

(47) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(49) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(2,4-dibenzyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(54) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(73) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(88) 2[4-butyl-2-(3,4-dichloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2yl-ethyl]acetamide

(90) 2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide

(91) 2{2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]acetylamino}-3-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide; and

(93) 3-(1-carbamimidoyl-piperidine-3-yl)-2-[2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino]-N-methyl-propionamide.

Compounds of the invention may be used in the treatment and/or prophylaxis of disorders mediated by serine proteases such as viral serine proteases i.e. HSV, CMV, HCV; those serine proteases involved in coagulatioin pathways i.e. thrombin, protein C / activated protein C, factor VIIa, IXa and Xa.

Compounds of the invention may also be used in the treatment and prophylaxis of angiogenesis and tumour metastasis. In a particular embodiment, the compounds are used in the prophylaxis and/or treatment of thrombotic disorders mediated by the activity of thrombin. Such thrombotic disorders include venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial infarction and cerebral infarction. Methods of treatment or prophylaxis according to the invention comprise administering to a mammal, more particularly human, an effective amount of compounds of the present invention. By "effective" is meant an amount of the compound sufficient to alleviate or reduce the severity of the disorder as measured by parameters established for the particular indication i.e. blood flow (patency), clot size or density.

The compounds of the present invention may be used as anti-coagulants *in vitro* or *ex vivo* as in the case of contact activation with foreign thrombogenic surfaces such as is found in tubing used in extracorporeal shunts. The compounds of the invention may also be used to coat the surface of such conduits. To this end, the compounds of the invention are obtained as lyophilized powders, redissolved in isotonic saline and added in an amount sufficient to maintain blood in an anticoagulated state.

The therapeutic agents of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers, diluents or adjuvants. The proportion of each carrier, diluent or adjuvant is determined by the solubility and chemical nature of the compound, the route of administration, and standard pharmaceutical practice. For example, the compounds may be injected parenterally; this being intramuscularly, intravenously, or subcutaneously. For parenteral administration, the compound may be used in the form of sterile solutions containing other solutes, for example, sufficient saline or glucose to make the solution isotonic. The compounds may be administered orally in the form of tablets, capsules, or granules containing suitable excipients such as starch, lactose, white sugar and the like.

The compounds may also be administered sublingually in the form of troches or lozenges in which each active ingredient is mixed with sugar or corn syrups, flavouring agents and dyes, and then dehydrated sufficiently to make the mixture suitable for pressing into solid form. The compounds may be administered orally in the form of solutions which may contain colouring and/or flavouring agents.

Physicians will determine the dosage of the present therapeutic agents which will be most suitable. Dosages may vary with the mode of administration and the particular compound chosen. In addition, the dosage may vary with the particular patient under treatment. For parenteral administration, typical dosage is about 0.01 to 500 mg/kg body weight per day, and preferably about 0.5 to 10 mg/kg body weight per day.

When the composition is administered orally, a larger quantity of the active agent will typically be required to produce the same effect as caused with a smaller quantity given parenterally.

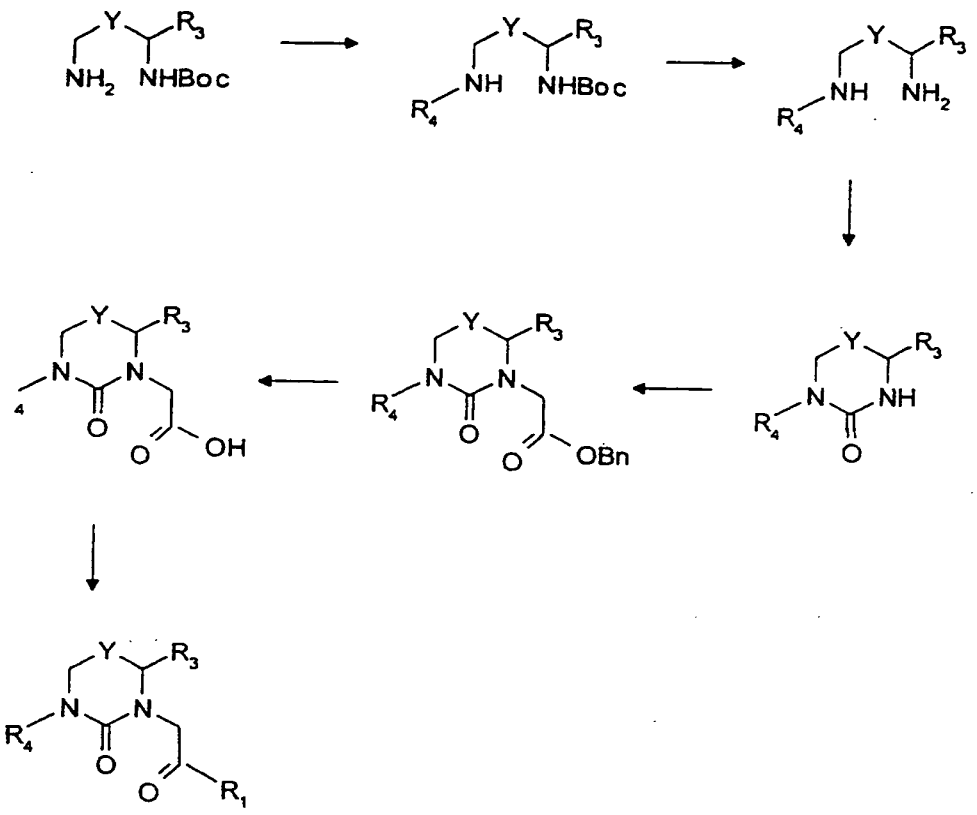
Compounds of the invention may be provided in "prodrug" form which are derivatives of said compounds that are converted to the active compound either prior to administration or in vivo upon administration and are encompassed by the present invention. Prodrugs of the present invention are prepared according to established organic synthetic techniques and include for example esters of carboxyl groups. Prodrug selection and preparation are described in detail in "The Practice of Medicinal Chemistry", Ed. C. G. Wermuth, Academic Press, New York, 1996 (in particular chapters 31 and 32) which is incorporated herein by reference. Also encompassed are salts of the compounds of the invention, particularly pharmaceutically acceptable salts such as inorganic salts i.e. chloride, bromide, sodium, calcium, and potassium; and organic salts i.e. acetate, citrate, maleate, tartrate and mesylate. Pharmaceutically acceptable salts and their preparation are described in detail in Wermuth (supra)

incorporated herein by reference.

Compounds of the present invention may be prepared according to established organic chemistry techniques from starting materials that are commercially available or themselves are readily prepared. According to one general method, the lactam portion of the molecule is 1) reacted with t-Bu bromoacetate followed by 2) ester hydrogenolysis to give monocyclic acid intermediate which is in turn 3) coupled by routine amidation to the polar amino acid residue R_1 to achieve the final compound. Various substituents may be introduced on the lactam or the polar amino acid residue R_1 either prior or subsequent to coupling.

In a particular embodiment, when W is N-R_4, the following general synthetic scheme may be employed.

Scheme 1



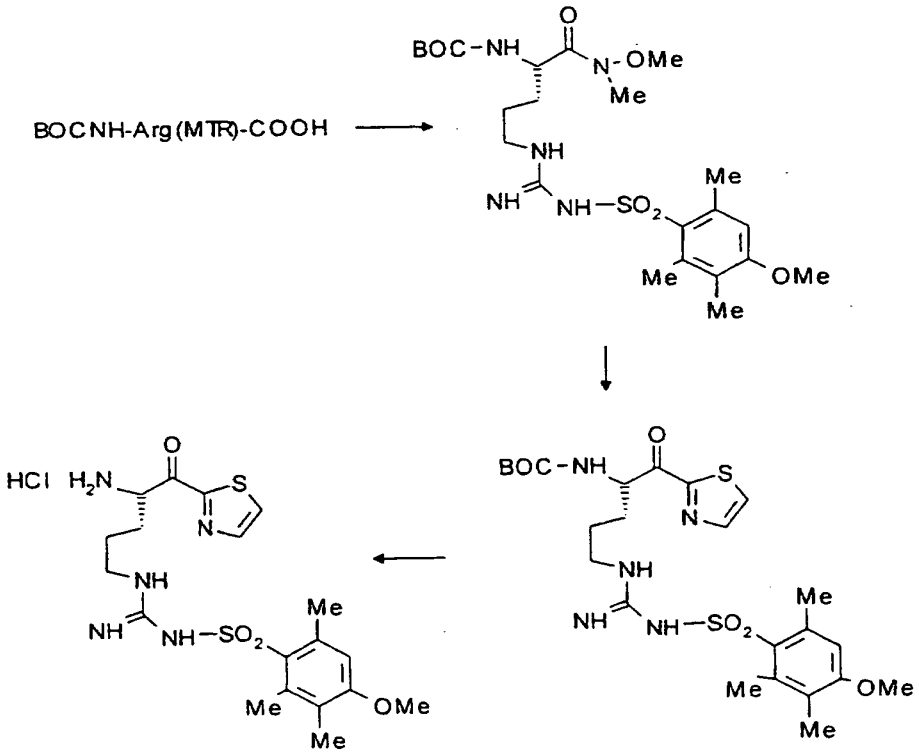
Briefly, monoprotected diaminopropane (Aldrich) may be substituted with a group according to R_4, for example alkylated (reductive amination: J. Org. Chem., 1996, 61:3849) with hydrocinnamaldehyde. The protecting group of the primary amine is removed and the di-amine is cyclized into a urea using triphosgene. The urea is alkylated with benzyl bromoacetate, followed by ester hydrogenolysis to give an acid intermediate which may then be coupled by amidation to an R_1 substituent. It will be appreciated that substituents may also be introduced on the cyclic urea prior to coupling with R_1 using conventional techniques in the art.

Where the compound of formula (I) is desired as a single isomer, it may be obtained either by resolution of the final

product or by stereospecific synthesis from isomerically pure starting material or any convenient intermediate. Resolution of the final product, or an intermediate or starting material therefor, may be effected by any suitable method known in the art: see for example, "Stereochemistry of Carbon Compounds", by E.L. Eliel (McGraw Hill, 1962), and "Tables of Resolving Agents", by S.H. Wilen. Resolution of the final compound can also be achieved using established chiral HPLC techniques as described in "Chiral Separations", Eds. D. Stevenson and I.D. Wilson; "Chromatographic Enantioseparation", Ed. Stig G. Alenmark; and "Chromatographic Separations of Stereoisomers", Ed. Rex W. Souter, each of which is incorporated herein by reference.

To further assist in understanding the present invention, the following non-limiting examples of such thrombin inhibitory compounds are provided.

EXAMPLE 1a Synthesis of intermediate thiazoloarginine-MTR·HCl



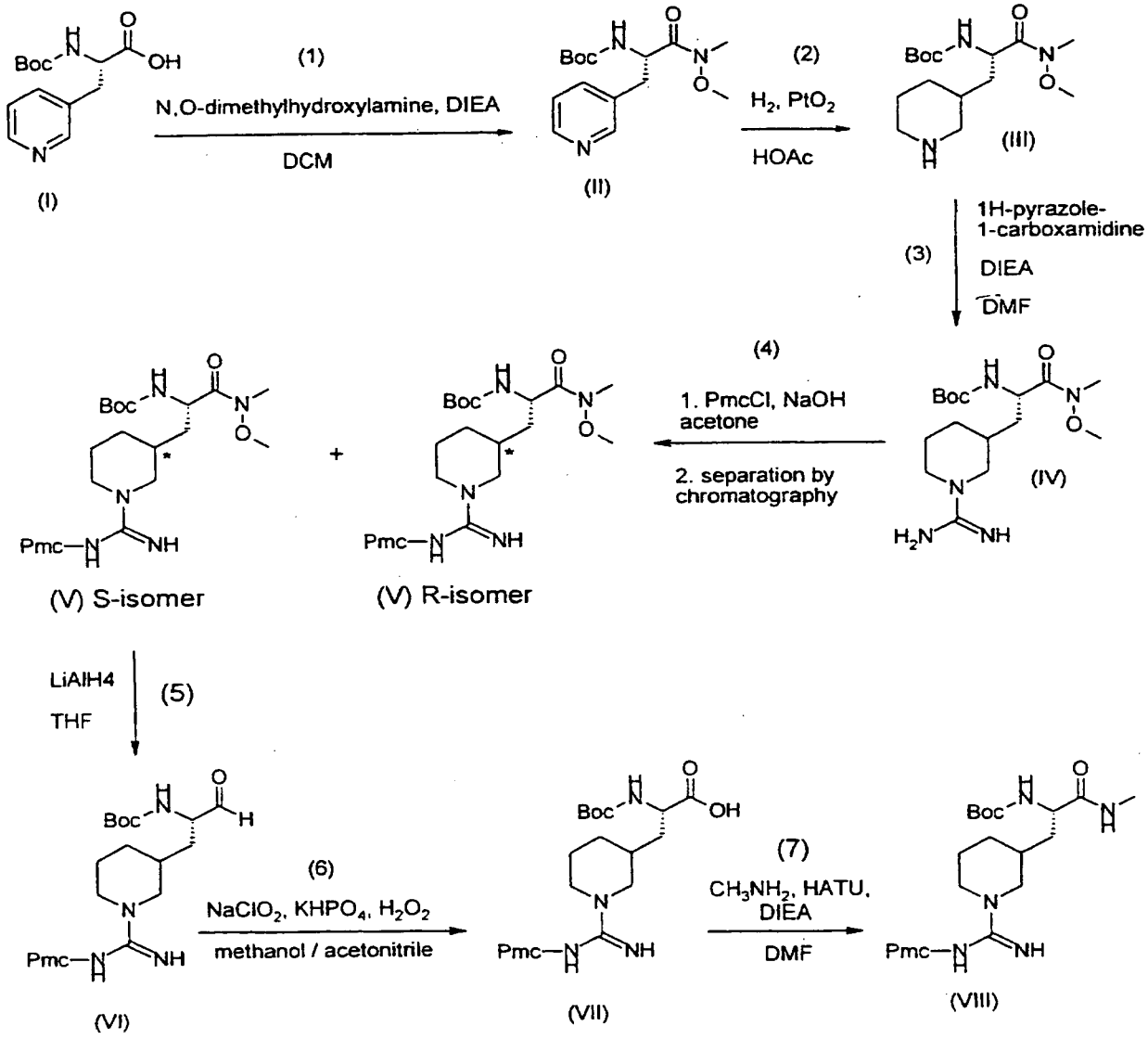
Step 1: To Boc-Arg(MTR)-OH (6.61g, 13.6mmol, Bachem) in dichloromethane (33mL) at 0°C was added N-methyl morpholine (1.65mL, 15.0mmol) then isobutyl chlorofomate (1.95mL, 15.0mmol) and stirred at 0°C for 30 minutes. N,O-dimethyl amine HCl (1.5g, 15.4mmol) and N-methyl morpholine (1.65mL, 15.0mmol) was added and stirred at 0°C for 45 minutes. The solution was diluted with ethyl acetate (150mL); washed with 1N HCl (2X80mL), brine (80mL), dried with sodium sulfate, filtered, and then removed solvent in vacuo, and purified with silica gel column (80% ethyl acetate in hexane to 100% ethyl acetate). BOC-Arg(MTR)-CO-N(Me)OMe was isolated 4,85g (67.5%) of product (1) as a white foam.

Step 2: To thiazole (1.95mL, 27.5mmol) and TMEDA (3.8mL, 25.2mmol, distilled from sodium) in THF (65mL, freshly distilled from potassium) at -78°C was added nBuLi in hexane (13.7mL, 24.7mmol, 1.8M) at a rate that raised the internal temperature to -50°C. Reaction flask was placed in dry ice/acetonitrile bath to give an internal temperature of -41°C. The solution was stirred for 25 minutes, cooled to -78°C and then BOC-Arg(MTR)-CO-N(Me)OMe (3.18g, 6.0mmol) in THF (33mL) was added and stirred for 45 minutes. Reaction was poured over a saturated ammonium chloride solution (200mL aq) and shook vigorously and then extracted with ethyl acetate (2X200mL). Organic phases were combined and washed with brine (150mL), dried with sodium sulfate, filtered, and then the solvent was removed in vacuo, purified with silica gel column (70% ethyl acetate in hexane to 100% ethyl acetate). BOC-Arg-CO-thiazol-2-yl was isolated (3.1g, 93%) as a white foam.

Step 3: To BOC-Arg-CO-thiazol-2-yl was added ethyl methyl sulfide (2.3mL, 25.4mmol) then 4M HCl in dioxane (20mL) and stirred at room temperature for 40 minutes. A yellow, gummy precipitate formed and the supernatant was decanted. Ethyl acetate (40mL) was added and the gummy precipitate was stirred to change it to a fine granular precipitate. Precipitate was isolated by filtration and washed thoroughly with ethyl acetate (150mL) to give 3.0g of the intermediate thiazolo-Arg(MTR).HCl

In a like manner, the intermediate benzothiazolo-Arg(MTR).HCl may be prepared by incorporating benzothiazole instead of thiazole in step 2.

EXAMPLE 1b synthesis of intermediate 1-carbamimidoyl-piperidin-3-ylalanine



Step 1: To N$^{\alpha}$Boc-3-pyridylalanine (I) (10.5g, 39.5mmol) in methylene chloride (106mL) was added BOP reagent [(benzotriazol-1-yloxy tris-(dimethylamino)phosphonium hexafluorophosphate), 18.3g, 41.48mmol] and DIEA (7.56mL, 43.45mmol). The reaction mixture was stirred at room

temperature for twenty minutes and then was added N,O-dimethylhydroxylamine hydrochloride (3.85g, 39.5mmol) followed by DIEA (7.56mL). The reaction mixture stirred four hours and the solvents removed in vacuo. The residue was dissolved in ethyl acetate and washed with 1N NaOH (3X25mL), water (2X25mL) and brine (1X50mL), dried over sodium sulfate, filtered and the solvents removed in vacuo. The product was crystallized from ethyl acetate/hexane to yield 5.67 g of produt. The filtrate was chromatographed on silica gel eluted with 80% ethyl acetate/hexane to 100% ethyl acetate to yield 4.4g of product. Total yield 10.07g (82%) of the desired product (II).

Step 2: To (II) (4.4g, 14.2mmol)in acetic acid (100mL) was added PtO_2 (0.44g) and hydrogen gas in a Parr reactor. The reation was complete in twenty three hours. The catalyst was filtered and the reaction mixture concentrated in vacuo. The product was dissolved in water and lyophylized to yield 5.9g of the desired product as a sticky oil (III).

Step 3: To (III) (6.75g, 17.9mmol) in DMF (9mL) was added [(1H-pyrazole-1-carboxamidine hydrochloride) 2.6g, 17.9mmol] followed by DIEA (6.25mL, 35mmol). The reaction mixture was stirred four hours at room temp. then the sovents removed in vacuo. The product was triturated with ether several times and the ether layer decanted. The product (IV) was used unpurified in the subsequent reaction.

Step 4: To (IV) (0.56g, 1.56mmol) in acetone (6.8mL) at 0°C was added 4N NaOH (1.7mL) and PmcCl [(4methyloxy-2,3,6-trimethylbenzenesulfonyl chloride, 0.679g, 2.73mmol] in acetone (1.7mL). The reaction mixture was stirred at 0°C for 2.5 hours. 10% citric acid was added until pH 6.0. The solvents were removed in vacuo. The residue was extracted with ethyl acetate several times and the combined organic phases were washed with brine, dried over magnesium sulfate, filtered and the solvents removed in vacuo. The product was purified on silica gel eluted with ethyl acetate to yield 396mg (V) R-isomer and 211mg (V) S-isomer.

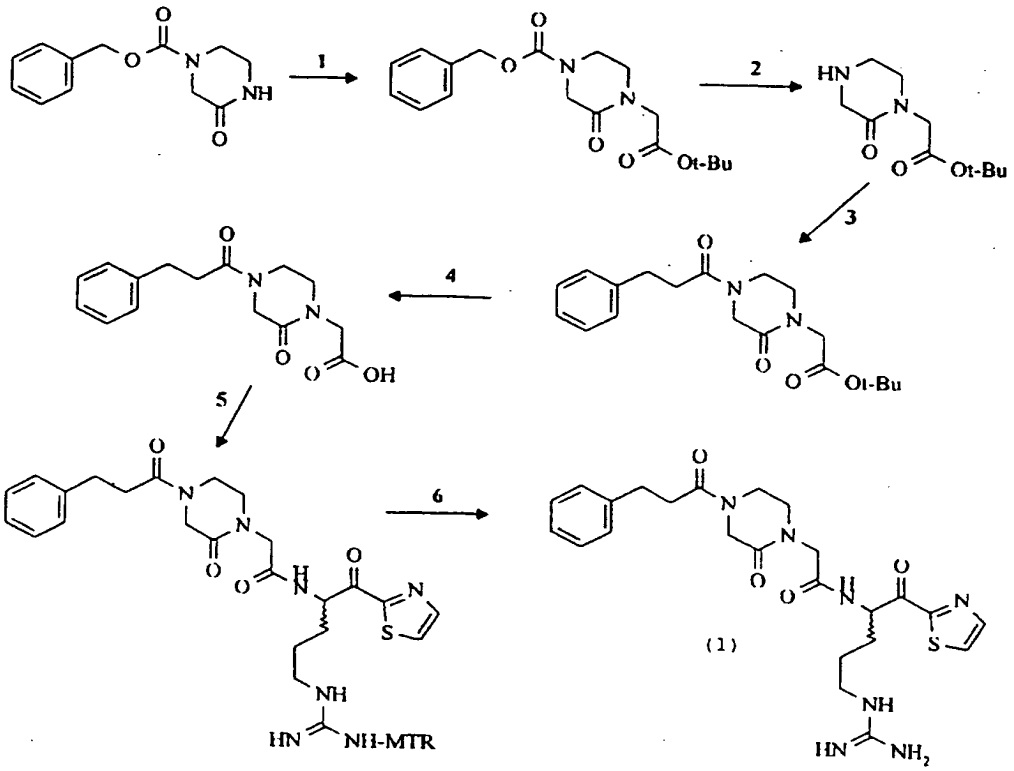
Step 5: To a solution of (V) (1.00g, 1.6mmol) in THF (5mL) at -78°C, was added 1M lithium aluminum hydride in THF (6.4mL, 6.4mmol) drop wise over 10 minutes. The reaction was stirred

at -78°C for an additioinal 30 minutes. 1M $KHSO_4$ (5.0mL) was added. The resulting solution was poured into a separatory funnel containing ethyl acetate and water (50mL each). The organic layer was separated, washed with brine (50mL) and dried with sodium sulfate. Evaporation to dryness gave 0.93g of (VI) as a white solid.

Step 6: To a solution of (VI) (0.90g, 1.58mmol) in methanol/acetonitrile at 0°C, was added $NaClO_2$ (0.40g, 3.53mmol), $KHPO_4$ (0.066g, 0.48mmol) and 30% aqueous H_2O_2. The reaction was then warmed to room temperature and stirred for an additional 4 hours. The reaction mixture was evaporated, the residue was taken up in H_2O, acidified with 10% HCl to pH 2.5 and extracted with ethyl acetate (2X50mL). The organic layer was washed with brine (50mL) and dried with sodium sulfate. After removal of solvent under reduced pressure, (VII) was obtained after crystallization with ethyl acetate/hexane (0.83g).

Step 7: A solution of (VII) (0.13g, 0.224mmol), HATU [(O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate), 0.085g, 0.225mmol], methylamine hydrochloride (0.020g, 0.31mmol) and DIEA (0.080mL, 0.46mmol) in DMF (2.0mL) was stirred at room temperature for 2 hours. The reaction mixture was poured into a separatory funnel containing ethyl acetate and saturated $NaHCO_3$ (20mL each). The organic layer was separated, washed with brine (50mL) and dried with sodium sulfate. After removal of solvent under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate) to give 0.130g of (VIII).

EXAMPLE 2 synthesis of compound (1) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide ditrifluoroacetate salt (1:1 mixture of isomers)



Step 1: To a suspension of NaH 60%/oil (256 mg, 1.5 eq) in dry THF (43 ml), at 0°C, under N_2, was added the oxo-piperazine carbamate (1.0 g, 4.27 mmols, Maybridge) in small portions. The reaction mixture was stirred at 0°C for 30 min and t-Bu bromoacetate (693 µL, 1.1 eq) was added. The ice bath was removed and the solution was stirred for 15 hr. Water (2 mL) was added carefully (to destroy the excess of NaH) and the solution was poured in EtOAc/H_2O. The phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with sat.aq. NaCl and dried over Na_2SO_4. The solids were filtered and the solvents evaporated. The crude product was purified by flash chromatography (silica gel, 1:1 hex/EtOAc) to give 1.43 g (4.12 mmols, 96%) of a white solid.

Step 2: To a solution of the carbamate from step 1 (1.43 g,

4.12 mmols) in dry MeOH (41 mL), at r.t., under N_2, was added Pd/C 10% (357 mg, 25% wt). The reaction mixture was placed under an H_2 atmosphere and stirred at r.t. for 60 min. The catalyst was filtered through Celite and the solvent was evaporated to give the amine (880 mg, 4.12 mmols, 100%) as a white solid.

Step 3: To a solution of the amine of step 2 (880 mg, 4.12 mmols) in dry DMF (41 mL), at r.t., under N_2, were added successively iPr_2NEt (1.43 mL, 2 eq), 3-phenylpropionic acid (648 mg, 1.05 eq) and BOP (2.72 g, 1.5 eq). The solution was stirred at r.t. for 15 hr and was poured in EtOAc/H_2O. The phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with 10% citric acid (1x), sat.aq. $NaHCO_3$ (1x), sat.aq. NaCl (1x) and were dried over Na_2SO_4. The solids were filtered and the solvents evaporated. The crude oil was purified by flash chromatography (silica gel, 100% EtOAc) to give the amido-lactam t-butyl ester (1.27 g, 3.65 mmols, 89%)as a beige oil.

Step 4: To a solution of the amidolactam t-butyl ester from step 3 (1.27 g, 3.65 mmols) in dry CH_2Cl_2 (18 mL), at 0°C, under N_2, was added CF_3COOH (18 mL). The solution was stirred at 0°C for 15 min, and then at r.t. for 3hr. The solvents were evaporated and the residue was co-distilled with benzene (2x) to remove the excess CF_3COOH. The resulting yellow oil was dried in vaccuo (1.06 g, 3.65 mmols, 100%).

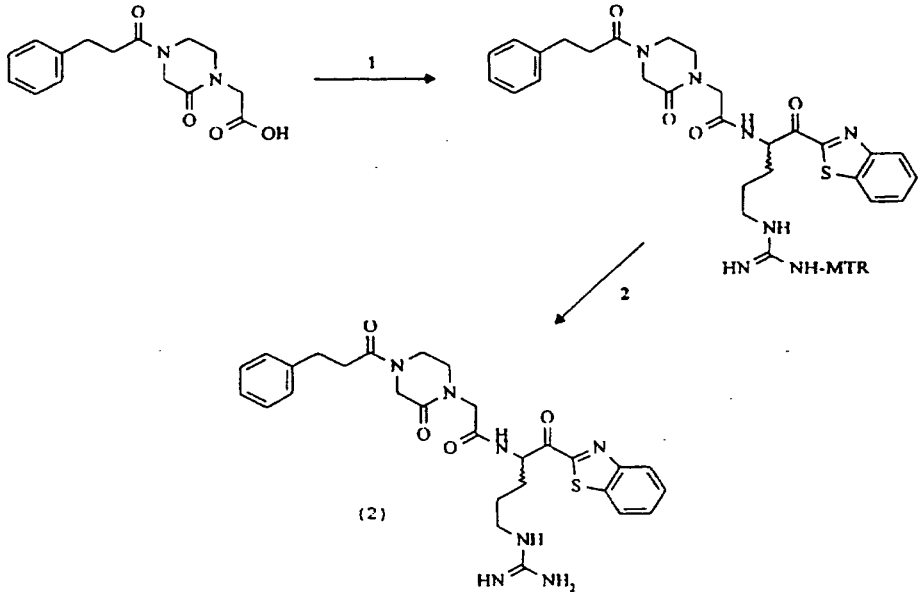
Step 5: To a solution of the acid from step 4 (134 mg, 0.46 mmol) in dry DMF (4.6 mL), at r.t., under N_2, were added successively thiazoloarginine-MTR·HCl (MTR = 1-methoxy-2,3,6-trimethylbenylsulfonyl) (273 mg, 1.2 eq), iPr_2NEt (241 µL, 3 eq), and BOP (307 mg, 1.5 eq). The solution was stirred at r.t. for 15 hr, after which it was poured in EtOAc/H_2O. The phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with 10% citric acid (1x), sat.aq. $NaHCO_3$ (1x), sat.aq. NaCl (1x) and were dried over Na_2SO_4. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, 90:8:2 EtOAc/MeOH/NH_4OH conc.) to give the guanidino-protected product (217 mg, 0.299 mmol, 65%)

as a yellow solid.

Step 6: To a solution of the guanidino-protected product from step 5 (211 mg, 0.29 mmol) in CF_3COOH (4 mL), at 0°C, under N_2, was added MeSPh (10% vol of TFA). The solution was stirred at 0°C for 30 min, then at r.t. for 4 hr. The TFA was evaporated down to a minimum volume and Et_2O (20 mL) was added. The suspension was stirred vigorously for 10 min. The solids were filtered, rinsed with Et_2O and dried in vaccuo. The crude product was purified by HPLC (15% CH_3CN/H_2O → 50% CH_3CN/H_2O, 180 min). The salt of compound (1) was obtained as a white solid (70 mg, 0.094 mmol, 24%).

^1H NMR (DMSO-d_6, 400 Mhz): δ 8.60 (d, 1H, J= 7.0), 8.28 (d, 1H, J= 2.9), 8.19 (d, 1H, J= 2.9), 7.60 (t, 1H, J= 5.5), 7.27-7.16 (m, 5H), 7.40-6.80 (bs, 4H), 5.42 (m, 1H), 4.16-3.96 (m, 4H), 3.65 (m, 2H), 3.32 (m, 1H), 3.27 (m, 1H), 3.11 (q, 2H, J= 6.6), 2.80 (t, 2H, J= 7.6), 2.65 (m, 2H), 1.90 (m, 1H), 1.64-1.55 (m, 3H).

EXAMPLE 3 synthesis of compound (2) N-[1-(Benzothiazole-2 carbonyl)-4-guanidino-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide trifluoroacetate salt (1:1 mixture of isomers)



Step 1: 2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetic acid was coupled with benzothiazoloarginine-MTR·HCl according to the procedures described in step 5 of example 2 to give the guanidino-protected final compound.

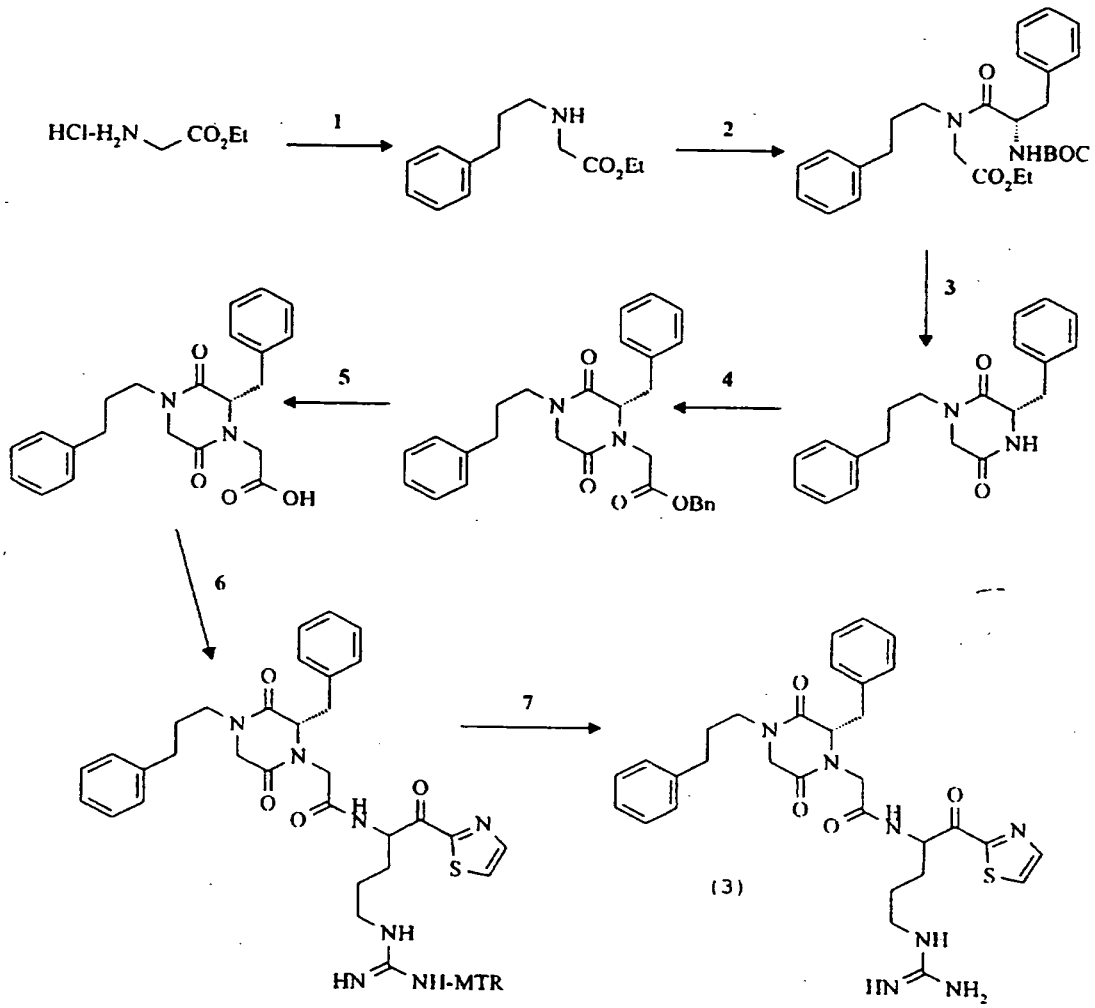
Step 2: The guanidino-protected product of step 1 was deprotected according to the procedures described in step 6 of example 2 (omitting addition of MeSPh) to give the final compound (2).

Purification: HPLC (20% CH_3CN/H_2O → 50% CH_3CN/H_2O, 240 min.)

^1H NMR (DMSO-d_6, 400 MHz): δ 8.71 (d, 1H, J= 6.7), 8.26 (m, 2H), 7.67 (m, 2H), 7.44 (m, 1H), 7.27-7.13 (m, 5H), 5.52 (m, 1H), 4.17-3.97 (m, 4H), 3.63 (m, 2H), 3.31 (m, 2H), 3.13 (q, 2H, J= 6.1), 2.79 (t, 2H, J= 7.5), 2.64 (t, 2H, J= 8.5), 1.95 (m, 1H), 1.71 (m, 1H), 1.58 (m, 2H).

EXAMPLE 4 synthesis of compound (3) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-

(thiazole-2-carbonyl)-butyl]-acetamide (1:1 mixture of isomers)



Step 1: To a solution of the glycine-OEt-HCl (499 mg, 3.58 mmol) in anh. EtOH (36 mL), at r.t., under N_2, were added hydrocynnamaldehyde (471 µL, 1 eq) and $NaBH_3CN$ (225 mg, 1 eq). The solution was stirred at r.t. for 18 hr. The EtOH was evaporated and the residue was poured in CH_2Cl_2/H_2O. The phases were separated and aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic extracts were dried over Na_2SO_4, the solids were filtered and the solvent evaporated. The crude oil was purified by flash chromatography (silica gel, 1:1 Hex/EtOAc) to give 377 mg (48%) of the pure amine.
Step 2: (3-phenyl-propylamine)-acetic acid ethyl ester was coupled with Boc-phenylalanine according to the procedure described in step 3 of example 2. Purification: flash

chromatography (silica gel, 8:2 Hex/EtOAc).

Step 3: To a solution of the BOC-carbamate from step 2 (776 mg, 1.66 mmol) in anh. dioxanne (8 mL), at r.t., under N_2, was added 4N HCl/dioxanne (0.1 M: 16 mL). The solution was stirred at r.t. for 4 hr. The solvent was evaporated and the oil dried under reduced pressure. The oil obtained was dissolved in H_2O (15 mL) and $NaHCO_3$ (700 mg, 5 eq) was added. The solution was heated at 60°C for 15 hr. A white precipitate was formed. The suspension was cooled to r.t. and the solid was filtered and then dried under vacuum to get 437 mg (82%) of the pure bi-lactam.

Step 4: To a suspension of 60% NaH/oil (81 mg, 1.5 eq) in anh. THF (13.5 mL), at 0°C, under N_2, was added the bi-lactam of step 3 (437 mg, 1.36 mmol), in small portions. The suspension was stirred at 0°C for 10 min, then at r.t. for 20 min. $BrCH_2CO_2Bn$ (236 µL, 1.1 eq) was added and the reaction mixture was stirred at r.t. for 18 hr. Water (10 mL) was added carefully to destroy the excess NaH and the reaction mixture was poured in EtOAc/H_2O. The layers were separated and the aqueous phase was extracted with EtOAc (2x). The combined organic extracts were washed with sat.aq. NaCl and dried over $MgSO_4$. The solids were filtered and the solvent evaporated. The crude product was purified by flash chromatography (silica gel, 6:4 Hex/EtOAc) and the final bi-lactam was obtained as a white solid (427 mg, 67%).

Step 5: To a solution of the ester from step 4 (427 mg, 0.91 mmol) in anh. MeOH (9.0 mL), at r.t., under N_2, was added Pd/C 10% (100 mg, 25% wt.). The black suspension was placed under an atmosphere of H_2 and was stirred for 60 min. The catalyst was filtered through Celite and was rinsed with MeOH. The solvent was evaporated and the resulting white solid was dried under vacuum: 338 mg (98%).

Step 6: The acid from step 5 was coupled with thiazolo-arginine-MTR·HCl according to the procedures described in step 5 of example 2 to give the guanidino-protected final compound. Purification: flash chromatography (silica gel, 2% MeOH/EtOAc)

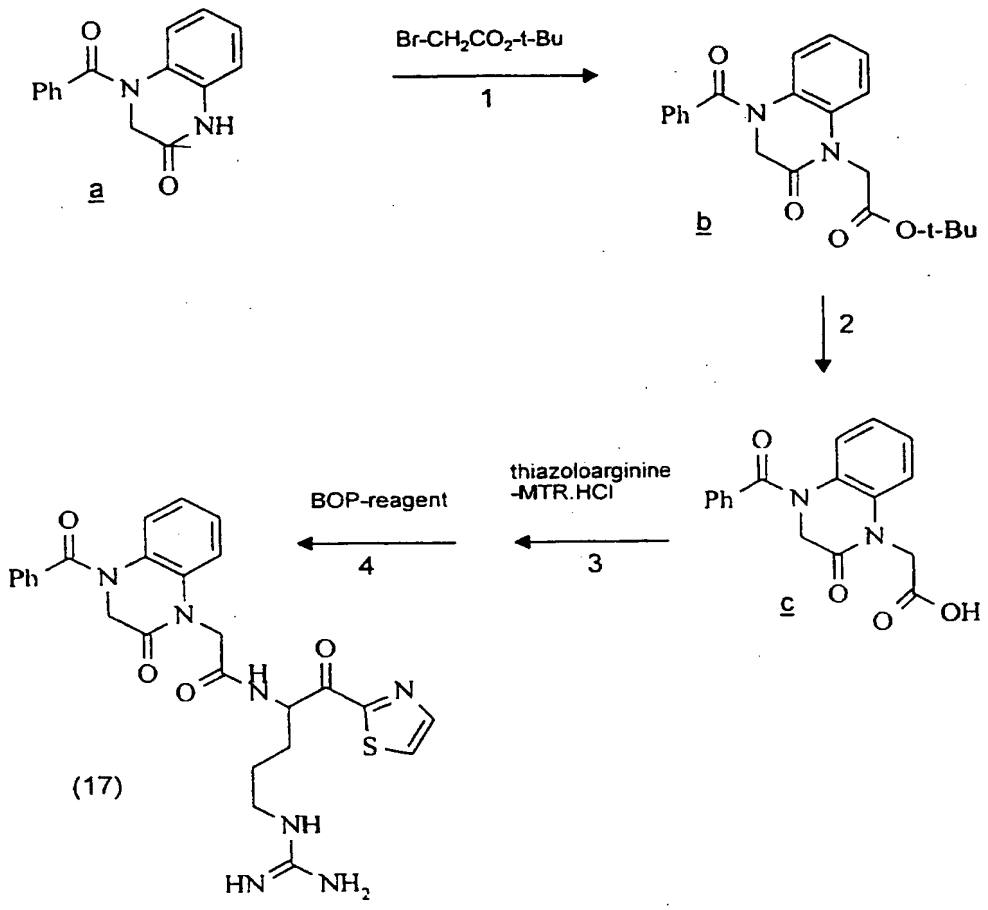
Step 7: The guanidino-protected final compound of step 6 was deprotected using standard HF cleavage to give final compound

(3) as a crude oil. The brown oil obtained was dissolved in 10% AcOH/H_2O. The aqueous phase was washed with Et_2O (2x) and evaporated to dryness.

Purification: HPLC (20% CH_3CN/H_2O, 20 min; 20% CH_3CN/H_2O → 50% CH_3CN/H_2O, 180 min, 5 ml/min) 68 mg of final compound was obtained as a white powder (0.095 mmol: 70%).

^1H NMR (DMSO-d_6, 400 MHz): δ 8.68 (d, 1H, J= 7.1), 8.29 (t, 1H, J= 3.0), 8.19 (t, 1H, J= 3.0), 7.46 (m, 1H), 7.29-7.07 (m, 10H), 5.42 (q, 1H, J=7.3), 4.47 (dd, 1H, J= 16.1), 4.17 (dt, 1H, J= 4.3, 16.1), 3.79-3.27 (m + H_2O), 3.15-2.97 (m, 4H), 2.63 (dd, 1H, J= 9.8, 17.1), 2.50-2.43 (m + DMSO), 1.89 (m, 1H), 1.67-1.53 (m, 5H).

EXAMPLE 5 synthesis of compound (17) 2-(4-benzoyl-2-oxo-3,4-dihydro-2H-quinoxalin-1-yl)-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide



Step 1: To a NaH suspension (0.24g, 5.9mmol) in THF (50mL) at 0°C was added compound a (1.0g, 3.96mmol, Maybridge) in small portions. The reaction was stirred for 30 minutes followed by addition of tert-butyl-2-bromoacetate (0.7mL, 4.0mmol). The reaction was allowed to stir overnight at ambient termperature followed by standard workup to give compound b.

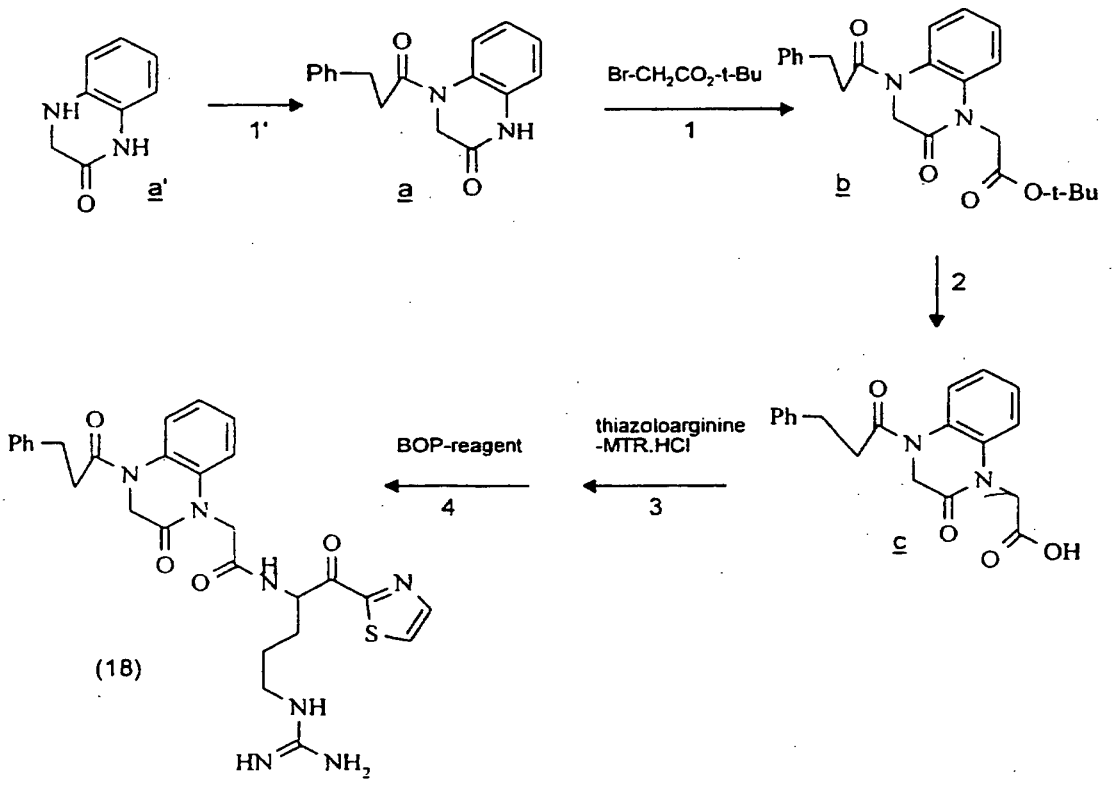
Step 2: To compound b (0.67mg, 1,83mmol) was added EtSMe (0.3mL) followed by TFA (10mL) at ambient temperature. The reaction was allowed to stir for 3h. The solvent was removed then added 10% aq.NaOH. The mixture was extracted with EtOAc and the aqueous layer acidified with powdered $KHSO_4$, followed by extraction with DCM. Drying the organic layer with $MgSO_4$

followed by evaporation of solvent yeilded the acid c.

Step 3: A mixture of c (0.235g, 0.758mmol) and thiazoloarginine-MTR.HCl (0.4g, 0.755mmol) was dissolved in DMF (20mL). The reaction was made basic using NMM then BOP-reagent (0.37g, 0.8mmol) was added. Reaction mixture was then stirred over night. Standard workup followed by column chromatography (1/1 EtOAc/Hex, v/v) yielded the product e.

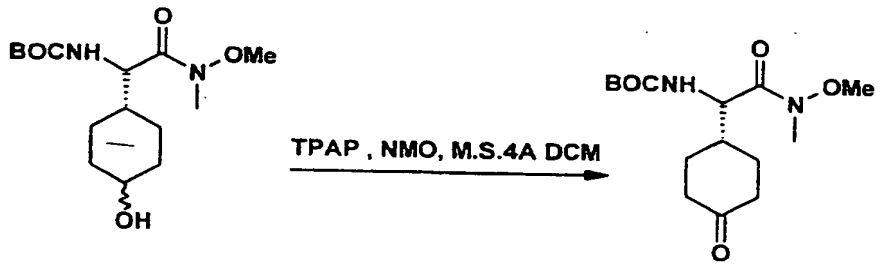
Step 4: A mixture of e (0.14g, 0.19mmol) was dissolved in TFA (2mL) and thioanisole (0.2mL) was added. The reaction stirred at room temperature for 6 hours then ether was added to precipitate the white powder which was purified by RP-TLC (0.5mm, Sigma; H2)/MeOH/TFA 80/80/5mL, v/v) to give 30mg of final compound (17).

EXAMPLE 6 synthesis of compound (17) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-3,4-dihydro-2H-quinoxalin-1-yl]-acetamide

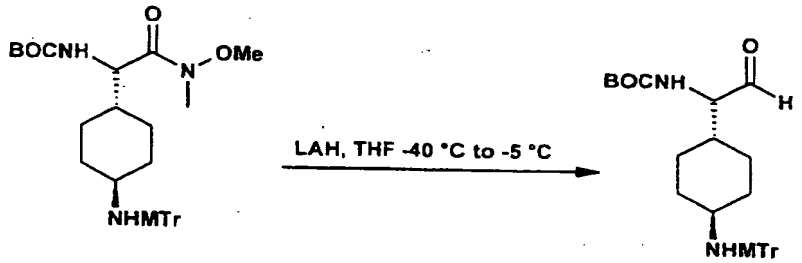


Step 1': To starting compound a (1.0g, 6.75mmol, Maybridge) at 0°C was added hydrocinnamoyl chloride (1.1mL, 3.96mmol) slowly then stirred at RT for 2h then added brine (50mL) to precipitate the light brown solid which was filtered and washed repeatedly with ether and hexane to give compound b. Subsequent step were performed in the same manner as steps 1-4 of example 5 to yield final compound (18).

EXAMPLE 7 synthesis of compound (96) 4-{2-Carboxy-2-oxo-1-[2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl)-acetylamino]-ethyl}-amino-cyclohexane

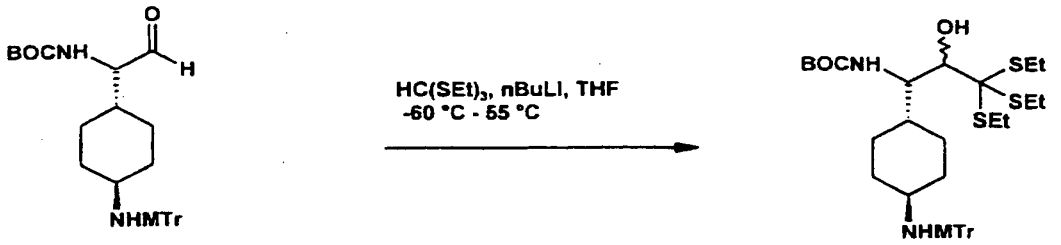


Step 1: To a mixture of the alcohol (21.7 g; 0.686 mol) and powdered molecular sieves 4A (40 g) in methylene chloride (500 mL) was added NMO (N-methyl morpholine oxide 17 g; 0.14 mol) followed by TPAP (tetrapropyl ammonium perruthenate 2.0 g). The mixture was stirred at room temperature for 40 minutes and then filtered on celite pad and washed thoroughly with dichloromethane. Silica gel was added to the filtrate and solvent was evaporated *in vacuo*. The adsorbed product was purified on silica gel (EtOAc 60 %, hexanes 40 %) to yield the pure ketone (15.7 g; 73 %) as a white solid.

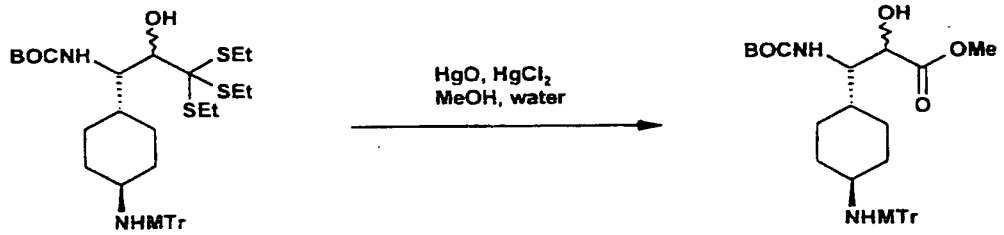


Step 2: To a solution of the amide (1.16 g, 2.21 mmols) in THF (30 mL) was added at -40 °C a 1.0 M solution of LAH in ether (2.9 mL). The solution was warmed to ~ -5 °C - 10 °C and stirred for 50 minutes. The solution was cooled to ~ -25 °C and quenched with 1 M aqueous solution of $KHSO_4$ (10 mL). The mixture was stirred at 0 °C for 40 minutes then brine was added (30 mL). The organic phase was separated and the aqueous layer extracted with ether (2 x 30 mL). The combined organic layers were washed successively with cold 1.0 M aqueous HCl

(20 mL), cold $NaHCO_3$ (s) (20 mL), cold brine (20 mL) then dried ($MgSO_4$). Evaporation of the solvent left a white foamy solid (952 mg; 92 %) that was used in the next step without further purification.

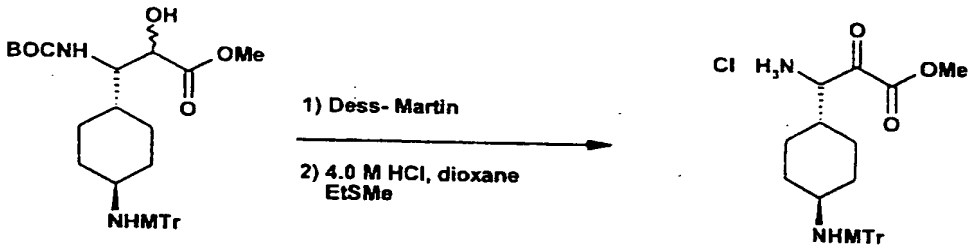


Step 3: To a solution of ethyl orthothioformate (2.7 mL; 14 mmols) in THF (30 mL) was added at - 60 °C - 55 °C n-BuLi in hexanes (1.3 M, 9.0 mL, 12 mmols). The solution was stirred at - 60 °C - 55 °C for 30 minutes then a solution of the aldehyde (932 mg; 2.00 mmols) in THF (10 mL) was added so that the temperature was maintained at - 60 °C - 55 °C. The solution was then stirred at - 40 °C for 1.5 hours then quenched at this temperature with a saturated solution of ammonium chloride in water (25 mL) and ether (30 mL) was added. The organic layer was separated and the aqueous phase was extracted with ether (2 x 30 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Purification on silica gel (EtOAc 25 % to 30 % in hexanes) afforded the desired product (975 mg, 73 %) as a mixture of isomers.

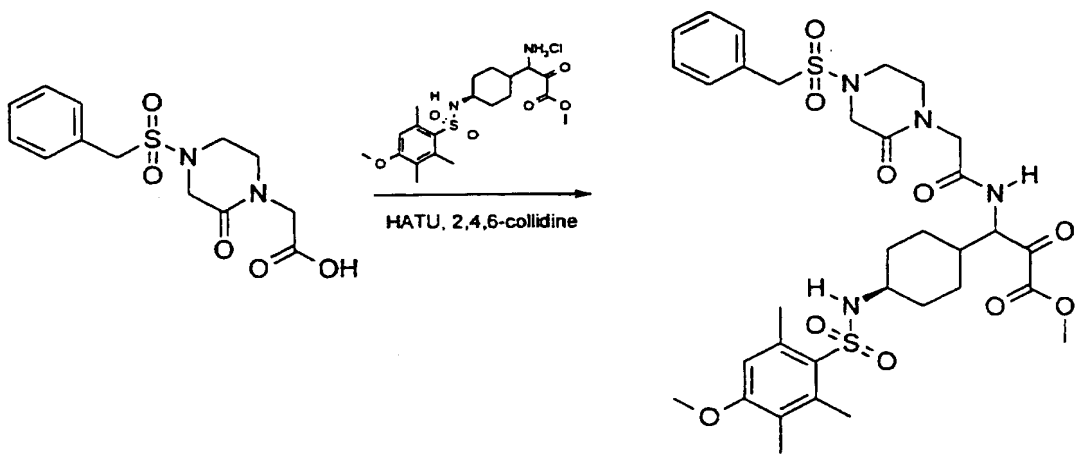


Step 4: To a solution of the orthothioformate (2.56 g; 3.85 mmols) in methanol (69 mL) and water (4 mL) was added HgO (732 mg) and mercuric chloride (2.69 g). The mixture was stirred at room temperature for 2 hours then at 60 °C for 30 minutes.

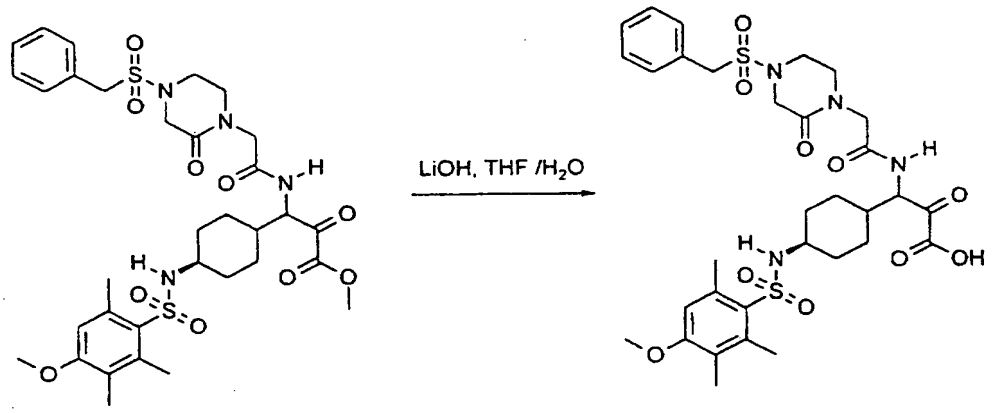
The mixture was filtered on a celite pad and washed with methanol (2 x 4 mL), and dichloromethane (3 x 20 mL). Water (80 mL) and dichloromethane (40 mL) was added to the filtrate and the organic layer was separated. The aqueous phase was extracted with dichloromethane (2 x 80 mL). The combined organic layers were washed with a 70 % aqueous ammonium acetate solution (200 mL) and the aqueous layer extracted with dichloromethane (2 x 200 mL). The combined organic layers were washed a saturated aqueous solution of ammonium chloride and dried ($MgSO_4$). Purification on silica gel (EtOAc 50%, hexanes 50%) afforded the hydroxy ester (1.33 g; 65 %) as a mixture of isomers.



Step 5: To a solution of the alcohol (812 mg; 1.54 mmols) in dichloromethane (100 mL) was added Dess-Martin reagent (3.0 g, 7.0 mmols). The resulting mixture was stirred at room temperature for 30 minutes then quenched with solution of sodium thiosulphate (15 g) in a saturated aqueous solution of $NaHCO_3$ (150 mL). The mixture was stirred for about 10 minutes and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ then dried ($MgSO_4$). Purification on silica gel (EtOAc 50%, hexanes 50%) afforded the keto ester (772 g; 95 %) pure as a white solid. This keto ester (772 mg) was dissolved in ethyl methyl sulfide (2 mL) and treated with 4.0 M HCl in dioxane (20 mL). The solution was stirred at room temperature for 30 minutes then volatiles were evaporated *in vacuo* to yield the crude deprotected amine (854 mg) which was used in the next step without further purification.

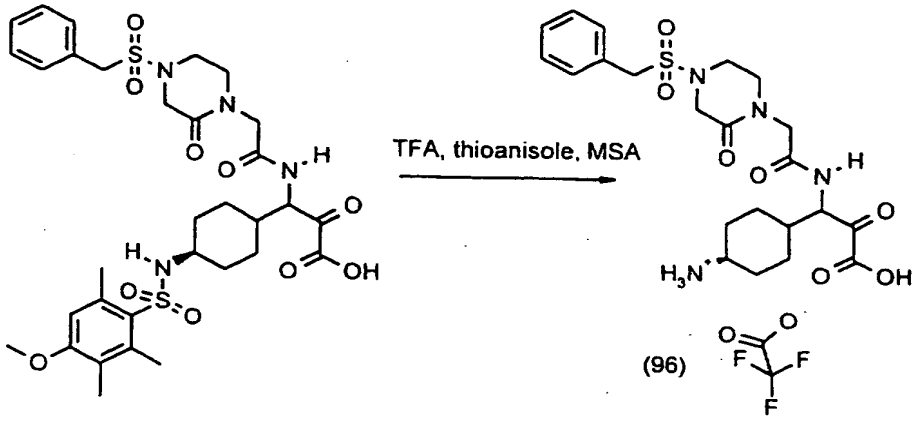


Step 6: To a solution of the acid (200 mg, 0.640 mmol) in dry DMF (7 mL) was added the amine (380 mg, 0.819 mmols) followed by collidine (0.8 mL) and by HATU (320 mg, 0.842 mmols). The solution was stirred at room temperature for 23 hours, poured into a 10% citric acid solution, extracted with ethyl acetate (3 times). The combined organic layers were washed successsively with a saturated solution of $NaHCO_3$, a 10 % citric acid solution, brine then fried ($MgSO_4$). The residue was purified on silica gel (EtOAC 100%) to afford the coupled product (265 mg, 57%).



Step 7: To a solution of the ester (265 mg, 0.367 mmols) in THF (10 mL) was added $LiOH \cdot H_2O$ (35 mg; 0.833 mmols) in water (10 mL). The solution was stirred at room temperature for one hour then poured into 5 % HCl (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were

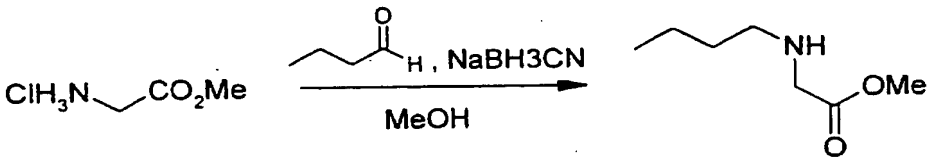
dried ($MgSO_4$) and evaporated to afford the acid (215 mg, 83 %) which was used in the next step without further purification.



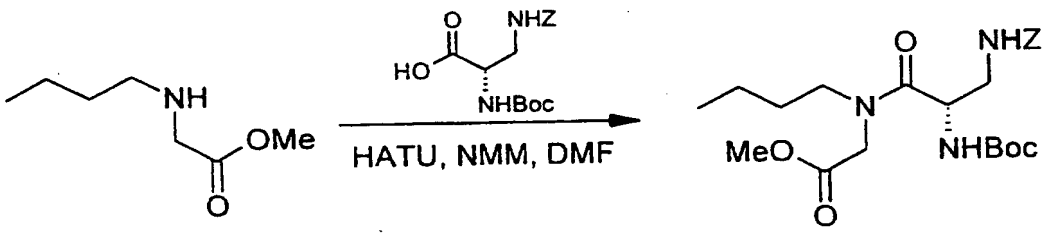
Step 11: To a solution of the protected compound (207 mg, 0.292 mmols) in TFA (10 mL) was added thioanisole (1 mL) and methanesulfonic acid (30 ml. 0.46 mmols). The solution was stirred overnight and TFA was evaporated. Ether was added to the residue and the resulting solid was filtered and washed several times with ether. This solid was purified by preparative HPLC to afford, after lyophilization, compound (98) (65 mg, 37%) as a mixture of diastereoisomers at the cyclohehyl moiety.

^{1} NMR (D_2O, 400 MHz) δ 7.38 (s, 5H), 4.96 (d, J = 4.7 Hz, 1H), 4.69 (s, 2H), 4.18 (d, J = 16.5 Hz, 0.5H), 4.14-4.06 (d, m, 0.5H), 3.97-3.91 (m, 0.5H), 3.95 (d, J = 16.5 Hz, 0.5H), 3.78 (s, 2H), 3.47-3.39 (m, 2H), 3.36-3.32 (m, 2H), 3.04-2.95 (m, 1H), 2.00-1.90 (m, 3H), 1.80-1.50 (m ,2H), 1.40-0.97 (m, 4H).

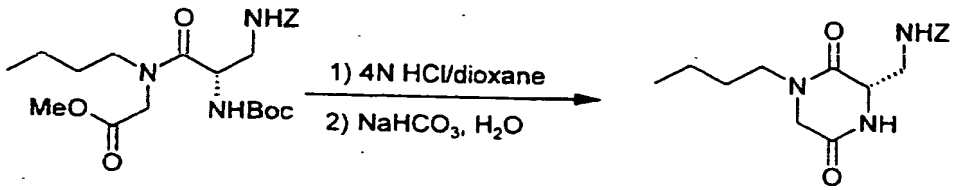
EXAMPLE 8 synthesis of compound (106) 2-[4-Butyl-3,6-dioxo-2-(phenylmethanesulfonylamino-methyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide



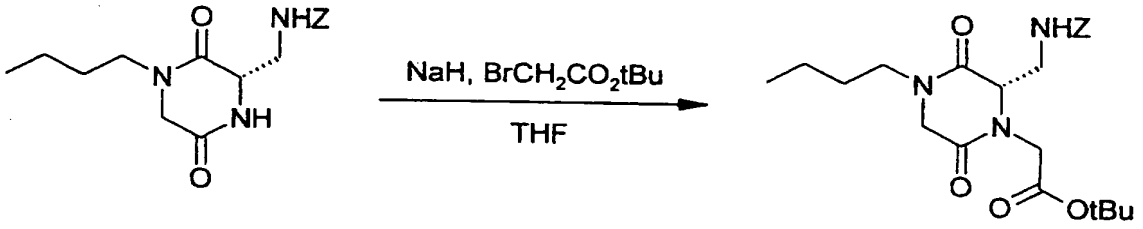
Step 1: To a solution of the amine (2.04 g, 16.24 mmol) in anh. MeOH (81 mL), at 0°C, under N_2, was added butyraldehyde (732 µL, 0.5 eq) and $NaBH_3CN$ (561 mg, 0.55 eq). The solution was stirred at 0°C for 30 min, then at r.t. for 18 hr. The MeOH was evaporated and the residue was poured in sat.aq. $NaHCO_3/CH_2Cl_2$. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic extracts were dried over $MgSO_4$, the solid were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography (silica gel, 4:6 Hex/EtOAc) to give the secondary amine as a clear oil (0.51 g, 3.53 mmol) in 43 % yield.



Step 2: To a solution of the amine (512 mg, 3.53 mmol) in anh. DMF (35 mL), at r.t., under N_2, was added the were added the acid (2.20 g, 1.2 eq), the NMM (776 µL, 2 eq) and HATU (1.61 g, 1.2 eq). The yellow solution was stirred at r.t. for 18 hr. The solvent was evaporated and the residue poured in EtOAc/H_2O. The phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with 10% citric acid (1x), sat.aq. $NaHCO_3$ (1x), sat.aq. NaCl (1x) and dried over $MgSO_4$. The solids were filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography (silica gel, 6:4 Hex/EtOAc) to give the amide as a clear oil (1.21 g, 2.61 mmol, 74%).

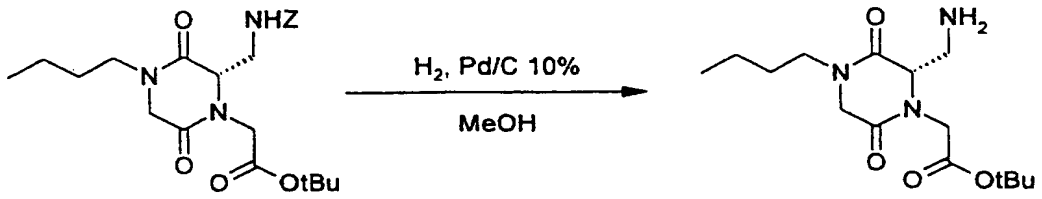


Step 3: 1) The ester-dicarbamate (1.21 g, 2.61 mmol) was dissolved in 4N HCl/dioxane. The solution was stirred at r.t. for 3 hr. The solvent was evaporated and the residue was dried *in vaccuo*. 2) The amine salt was dissolved in H_2O (26 mL) and $NaHCO_3$ (1.1 g, 5 eq) was added. A white solid precipitated immediatly. The suspension was heated at 60°C for 18 hr. It was brought down to r.t. and extracted with CH_2CL_2 (3x). The combined organic extracts were dried over $MgSO_4$, the solids were filtered and the solvent evaporated to give a crude oil which was purified by flash chromatography (silica gel, 3% MeOH/EtOAc). The final dioxopiperazine was obtained in 68% yield as a white solid (0.59 g, 1.78 mmol).

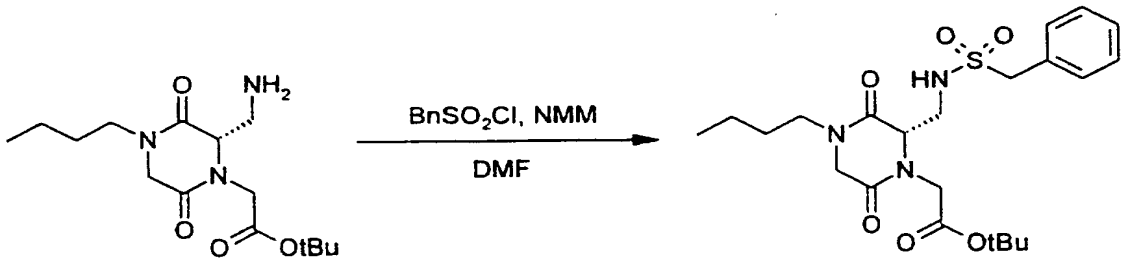


Step 4: To a suspension of NaH 60%/oil (64 mg. 1.1 eq), in dry THF (10.6 mL), at 0°C, under N2, was added a solution of the dioxopiperazine (486 mg, 1.46 mmol, in 2 mL of anh. THF). The flask was rinced with another 2 mL of anh. THF. The suspension was stirred at 0°C for 30 min, and then at r.t. for 30 min. BrCH2CO2tBu (30 µL, 1.1 eq) was then added and the solution/suspension was stirred at r.t. for 2 hr. Water (2 mL) was then carefully added in order to destroy the excess NaH. The THF was evaporated and the aqueous residue was poured in CH2Cl2/H2O. The phases were separated and the aqueous layer was exctracted with CH2Cl2 (2x). The combined

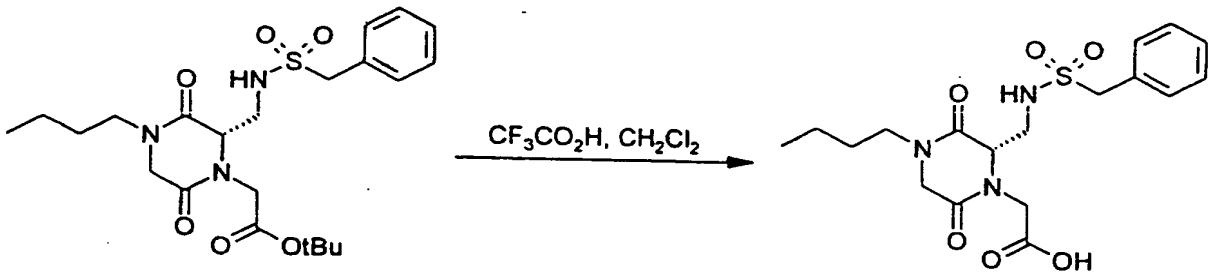
organic extracts were dried over MgSO4, the solid filtered and the solvent evaporated. The crude oil obtained was purified by flash chromatography (silica gel, 4:6 Hex/EtOAc) to give the ester as a white solid (463 mg, 1.04 mmol) in 71% yield.



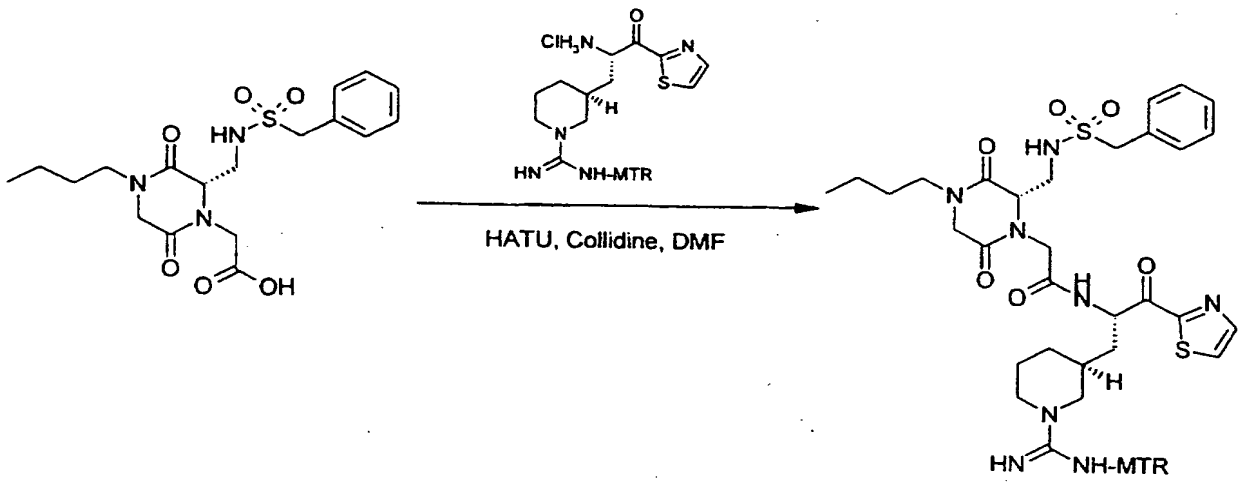
Step 5: To a solution of the carbamate (463 mg, 1.04 mmol) in anh. MeOH (10 mL), at r.t., under N_2, was added Pd/C 10% (115 mg, 25% wt). The black suspension was placed under an H_2 atmosphere and stirred at t.p. for 60 min. The catalyst was filtered through Celite and the Celite cake was rinced with MeOH. The solvent was evaporated and the residue was dried under vacuum to give the amine as a clear oil (333 mg, 0.96 mmol, 93%).



Step 6: To a solution of the amine (333 mg, 0.96 mmol) in anh. CH_2Cl_2 (9.6 mL), at t.p., under N_2, were added NMM (159 µL, 1.5 eq) and $BnSO_2Cl$ (193 mg, 1.05 eq). The solution was stirred at r.t. for 2 hr. It was then poured in 10% citric acid/CH_2Cl_2. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic extracts were dried over $MgSO_4$, the solids were filtered and the solvent evaporated to give a crude oil that was purified by flash chromatography (silica gel, 4:6 Hex/EtOAc). The benzylsulfonamide was obtained as a clear oil in 88% yield (396 mg, 0.85 mmol).

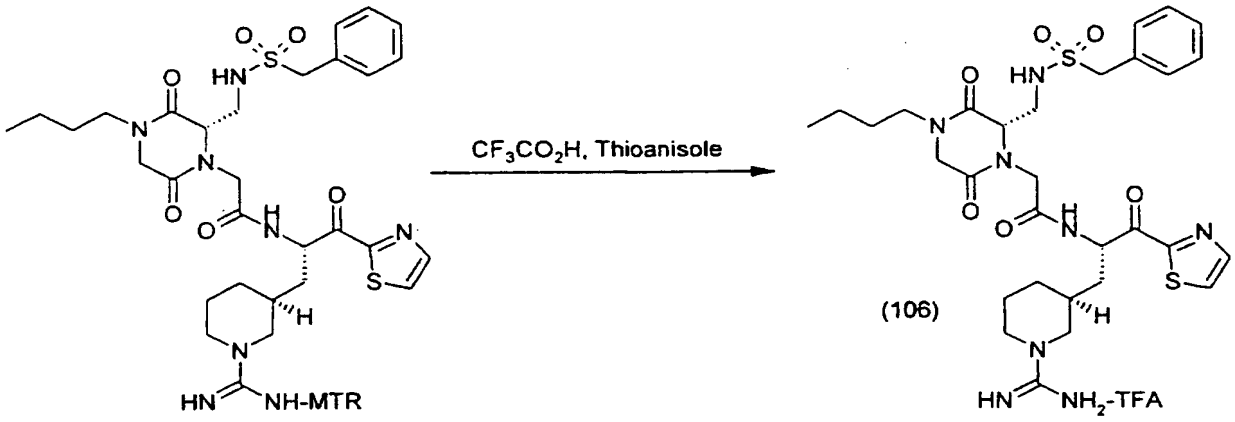


Step 7: To a solution of the ester (396 mg, 0.85 mmol) in anh. CH2Cl2 (4.25 mL), at 0°C, under N2, was added trifluoroacetic acid (4.25 mL). The solution was stirred at 0°C for 15 min, and then at r.t. for 2 hr. The solvents were evaporated and the residue dried under vacuum. The acid was obtainded in 100% yield as a yellow solid (349 mg, 0.85 mmol).



Step 8: To a solution of the acid (270 mg, 0.66 mmol) in anh. DMF (6.5 mL), at r.t., under N2, were added successively the arginine-mimic·HCl (382 mg, 1.1 eq), 2,4,6-collidine (347 µL, 4 eq) and HATU (299 mg, 1.2 eq). The solution was stirred at r.t. for 15 hr and was then poured in EtOAc/H2O. The phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic extracts were washed with 10% citric acid (1x), sat.aq. NaHCO3 (1x), sat.aq. NaCl (1x) and dried over MgSO4. The solids were filtered and the solvent evaporated to give a crude oil that was purified by flash chromatography (silica gel, 3% MeOH/EtOAc). The product was obtained as a yellow solid (349 mg, 0.39 mmol) in

60% yield.



Step 9: To a solution of the protected guanidine (349 mg, 0.39 mmol) in trifluoroacetic acid (10 mL), at r.t., under N_2, was added thioanisole (1 mL, 10% vol of TFA). The solution was stirred at r.t. for 3 hr. The TFA was evaporated and Et_2O (20 mL) was added to precipitate the guanidine salt. The solid was scraped off the wall of the flask and the suspension was stirred vigorously for 10 min. The solids were then filtered and dried under vacuum. The crude compound was purified by HPLC (20% CH_3CN/H_2O, 20 min ; 20% CH_3CN/H_2O → 50% CH_3CN/H_2O, 180 min ; 5 mL/min) to obtain 108 mg of the pure compound as a white solid (108 mg, 0.14 mmol, 35%). ^1H NMR (DMSO-d6, 400 MHz) : δ

EXAMPLE 9 Biological Assays

Thrombin Affinity

The affinity of inhibitors for thrombin was measured according to the procedures described in (DiMaio et al, J. Bio. Chem., 1990, 265:21698) Inhibition of amidolytic activity of human thrombin was measured fluorometrically using Tos-Gly-Pro-Arg-AMC as a fluorogenic substrate in 50 mM Tris-HCl buffer (pH 7.52 at 37°C) containing 0.1 M NaCl and 0.1% poly(ethylene glycol) 8000 at room temperature (Szewczuk et al., Biochemistry, 1992 31:9132).

The hydrolysis of the substrate by thrombin was monitored on a

Varian-Cary 2000™ spectrophotometer in the fluorescence mode (λeX = 383 nm, λem = 455 nm) or on a Hitachi F2000™ fluorescence spectrophotometer (λ_{ex} = 383 nm, λ_{em} = 455 nm), and the fluorescent intensity was calibrated using AMC. The reaction reached a steady-state within 3 minutes after mixing thrombin with the substrate and an inhibitor. The steady-state velocity was then measured for a few minutes. The compounds of this invention were also pre-incubated with thrombin for 20 minutes at room temperature before adding the substrate. The steady-state was achieved within 3 min and measured for a few min. The kinetic data (the steady-state velocity at various concentrations of the substrate and the inhibitors) of the competitive inhibition was analyzed using the methods described by Segel (1975). A non-linear regression program, RNLIN in the IMSL library (IMSL, 1987), LMDER in MINPACK library (More et al., 1980) or Microsoft™ Excell™ , was used to estimate the kinetic parameters (K_m V_{max} and K_i).

Arterial Thrombosis Model

The $FeCl_3$ induced injury to the carotid artery in rats was induced according to the method described by Kurz, K.D., Main, R.W., Sandusky, G.E., Thrombosis Research 60; 269-280, 1990 and Schumacher, W.A. et al. J. Pharmacology and Experimental Therapeutics 267; 1237-1242, 1993.

Male, Sprague-Dawley rats (375-410 g) were anesthetized with urethane (1500 mg\kg ip). Animals were laid on a 37°C heating pad. The carotid artery was exposed through a midline cervical incision. Careful blunt dissection was used to isolate the vessel from the carotid sheath. Using forceps, the artery was lifted to provide sufficient clearance to insert two small pieces of polyethylene tubing (PE-205*) underneath it. A temperature probe (Physitemp* MT23/3) was placed between one of the pieces of tubing and the artery. Injury was induced by topical application on the carotid artery above the temperature probe of a small disc (3 mm dia.) of Whatman* No.1 filter paper previously dipped in a 35%

solution of $FeCl_3$. The incision area was covered with aluminum foil in order to protect the $FeCl_3$ from degradation by light. The vessel temperature was monitored for 60 minutes after application of $FeCl_3$ as an indication of blood flow. Vessel temperature changes were recorded on a thermister (Cole-Palmer® Model 08533-41).

The time between the $FeCl_3$ application and the time at which the vessel temperature decreased abruptly (>2.4°C) was recorded and the mean occlusion time (MOT) of the vessel calculated. Inhibitor compounds were given as an i.v. bolus (0.75 mg/kg) followed immediately by an i.v. infusion (50 µg/kg/min. via femoral vein).

aPTT and TT

Blood (1mL) was collected in to sodium citrate (1:9; 3.8%) as an anticoagulant prior to treatment, 30 and 90 min. after the start of the infusion. All anticoagulated blood samples were centrifuged (12,000 x g for 3 min.) to obtain plasma for same day analysis. Activated partial thromboplastin time (aPTT) and thrombin time (TT) were measured at 37°C using a coagulometer (ST4 from Diagnostica Stago, Asnieres, France; American Bioproducts Company, Parsipanny, NJ). For aPTT measurements, citrated plasma (50uL) was incubated with reagent 1 (PTTAutomate; 00480, ST4 BIO; Diagnostica Stago) at 37°C for 180 sec. Clotting was initiated by adding 25mM $CaCl_2$ (50uL). For TT measurements, citrated plasma (200uL) was incubated at 37°C for 2 min. and the clotting time was initiated by adding Thrombin Prest (titrated calcium thrombin; 200uL; Diagnostica Stago). The time taken for the plasma to clot was then determined.

Table 1

Compound	Ki [IC_{50}] (nM)	MOT[1] (min)	aPTT[2] (sec)	TT[3] (sec)
(1)	35	24.3 ± 3.2	32.9 ± 2.54	175.5 ± 10.5
(2)	12	31.2 ± 5	31.7 ± 1.5	288 ± 30.8
(3)	10	23.83 ± 3.8	44 ± 0.92	298 ± 8.3
(6)	1220	-	-	-
(6a)	580	-	-	-
(6b)	7420	-	-	-

a fast moving isomer on HPLC

b slow moving isomer on HPLC

[1] baseline = 17.22 ± 0.6 minutes

[2] baseline aPTT = 18.1 ± 4 sec

[3] baseline TT = 46.7 ± 1.1 sec

Compound	Ki [IC_{50}] (nM)	Compound	Ki [IC_{50}] (nM)
(17)	240	(33)	140
(18)	1000	(34)	325
(20)	[130]	(35)	180
(21)	65	(36)	[750]
(22)	190	(37)	105
(23)	165	(38)	18
(24)	200	(39)	[1420]
(25)	98	(40)	195
(26)	[400]	(41)	[830]
(27)	74	(42)	825
(28)	55	(43)	55
(29)	40	(44)	130
(30)	30	(45)	[587]
(31)	75	(46)	[250]
(32)	43	(47)	[262]

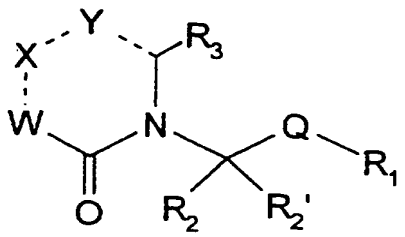
Compound	Ki [IC_{50}] (nM)	Compound	Ki [IC_{50}] (nM)
(48)	[990]	(62)	[810]
(49)	[1230]	(63)	[7200]
(50)	[6810]	(64)	[760]
(51)	[3980]	(65)	[210]
(52)	[1300]	(66)	[690]
(53)	[780]	(67)	[650]
(54)	[80]	(68)	[5860]
(55)	[110]	(69)	[170]
(56)	[210]	(70)	[350]
(57)	[110]	(71)	[368]
(58)	[1410]	(72)	[238]
(59)	[490]	(73)	1.2
(60)	[830]	(74)	[1640]
(61)	[1360]	(75)	[8690]

Compound	Ki [IC_{50}] (nM)	Compound	Ki [IC_{50}] (nM)
(76)	[88.7]	(93)	[229]
(77)	[984]	(94)	[1610]
(78)	[457]	(94a)	[610]
(79)	[283]	(94b)	[5130]
(80)	[1260]	(95)	[113]
(81)	495	(100)	25000
(82)	[3420]	(101)	50000
(83)	80	(102)	3000
(84)	55	(103)	2600
(85)	[880]	(104)	2500
(86)	140		

a fast moving isomer on HPLC
b slow moving isomer on HPLC

WE CLAIM:

1. A compound of formula (I):



(I)

wherein:

W and **X** are independently selected from CH-R_4, C-R_4, N-R_4, N, O, S, SO and SO_2, provided that at least one of W and X is selected from N-R_4, N, O, S, SO and SO_2;

Y is selected from CH-R_4, C-R_4 and C=O;

Q is selected from carbonyl, C=S and CH-R_4;

R_1 is a polar amino acid residue or derivative or analogue thereof optionally substituted with an amino acid, a peptide or a heterocycle;

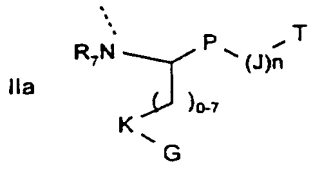
R_2 and R_2' are independently selected from H, halogen, C_{1-16} alkyl optionally substituted with C_{6-16} aryl, heterocycle or a C_{3-7} cycloalkyl group; and

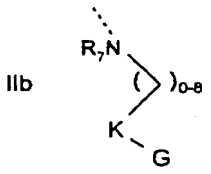
R_3 and R_4 are independently selected from H; NR_5R_6; carboxyl; C_{6-16} aryl or C_{3-7} cycloalkyl optionally substituted with C_{1-6} alkyl; C_{1-16} alkyl optionally interrupted by one or more heteroatom or carbonyl group and optionally substituted with OH, SH, NR_5R_6 or a C_{6-16} aryl, heterocycle or C_{3-7} cycloalkyl group optionally substituted with halogen, hydroxyl, carboxyl, C_{1-6} alkyl; an amino acid side chain; and a hydrophobic group; or

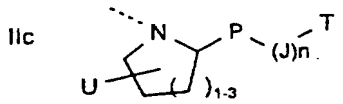
when Y is CH-R_4 or C-R_4 then R_3 and R_4 together with Y form a 5 or 6 member saturated or unsaturated carbocyclic ring;

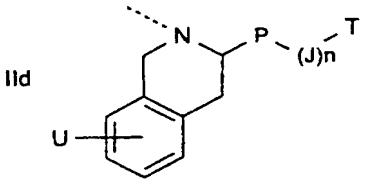
R_5 and R_6 are independently selected from H and C_{1-4} alkyl.

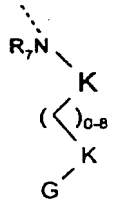
2. A compound according to claim 1, wherein R_1 is one of formula IIa to IId:











wherein:

R_7 is hydrogen or C_{1-6} alkyl;

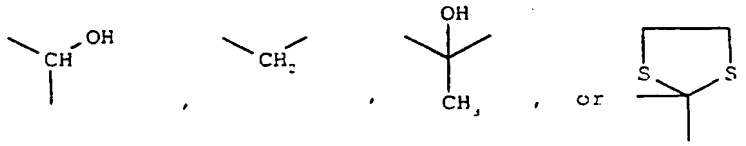
K is a bond or $-NR_7-$;

G is C_{1-4} alkoxy; cyano; $-NHR_8$; $-CH_2-NHR_8$; $-C(NH)-NHR_8$; $-NH-C(NH)-NHR_8$; $-CH_2-NH-C(NH)-NHR_8$; a C_{6-12} cycloalkyl or aryl substituted with cyano, $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NHR_8$, $-CH_2-NH-C(NH)-NHR_8$, halogen C_{1-4} alkyl, aryl or heterocycle; or a 5 or 6 member, saturated or unsaturated heterocycle or heterobicycle optionally substituted with cyano, $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NH_2$ $-CH_2-NH-C(NH)-NHR_8$, halogen C_{1-4} alkyl, aryl or heterocycle; provided that G is other than unsubstituted indole and when G is C_{6-12} cycloalkyl or aryl then G is substituted with at least one group selected from $-NHR_8$, $-CH_2-NHR_8$, $-C(NH)-NHR_8$, $-NH-C(NH)-NHR_8$ or $-CH_2-NH-C(NH)-NHR_8$;

U is cyano, $-NHR_8$, $-C(NH)-NHR_8$ or $-NH-C(NH)-NHR_8$;

R_8 is H, OH or NH_2;

P is a bond, -C(O)-, -C(S)- or a bivalent group:



J is C_{1-6} alkylene optionally substituted with OH, NH_2 and

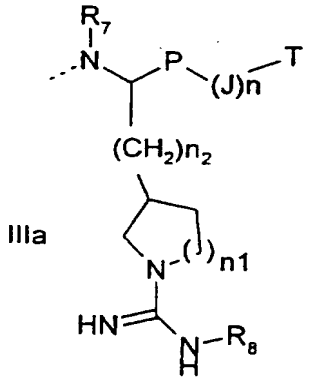
C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

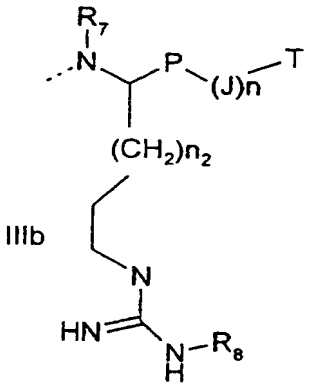
n is 0 or 1; and

T is H, OH, O-R_4, carboxyl, amino, a peptide chain, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, or heterocycle optionally substituted;

provided that R_1 is other than -$NHNH_2$.

3. A compound according to claim 2, wherein R_1 is selected from:



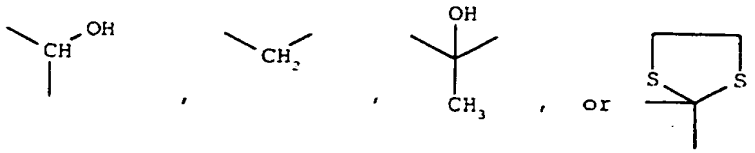


wherein:

R_7 is hydrogen or C_{1-6} alkyl;

R_8 is H, OH or NH_2

P is a bond, -C(O)-, -C(S)- or a bivalent group:

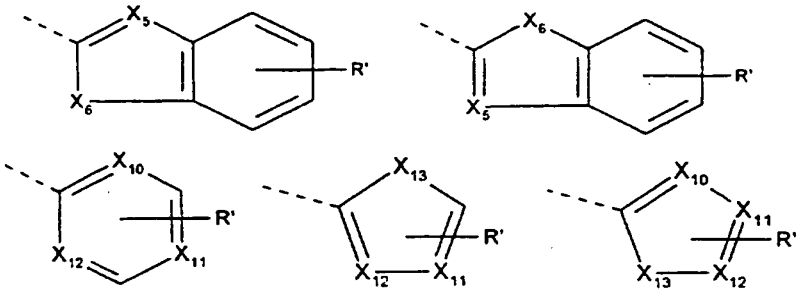


J is C_{1-6} alkylene optionally substituted with OH, NH_2 and C_{1-6} alkyl and optionally interrupted by a heteroatom selected from O, S and N;

n is 0 or 1; and

T is H, OH, O-R_4, carboxyl, amino, a peptide chain, C_{1-16} alkyl, C_{1-16} alkoxy, C_{6-20} aralkyl, or heterocycle optionally substituted.

4. A compound according to claim 3, wherein P is C(O), n is 0 and T is a heterocycle selected from the group consisting of:



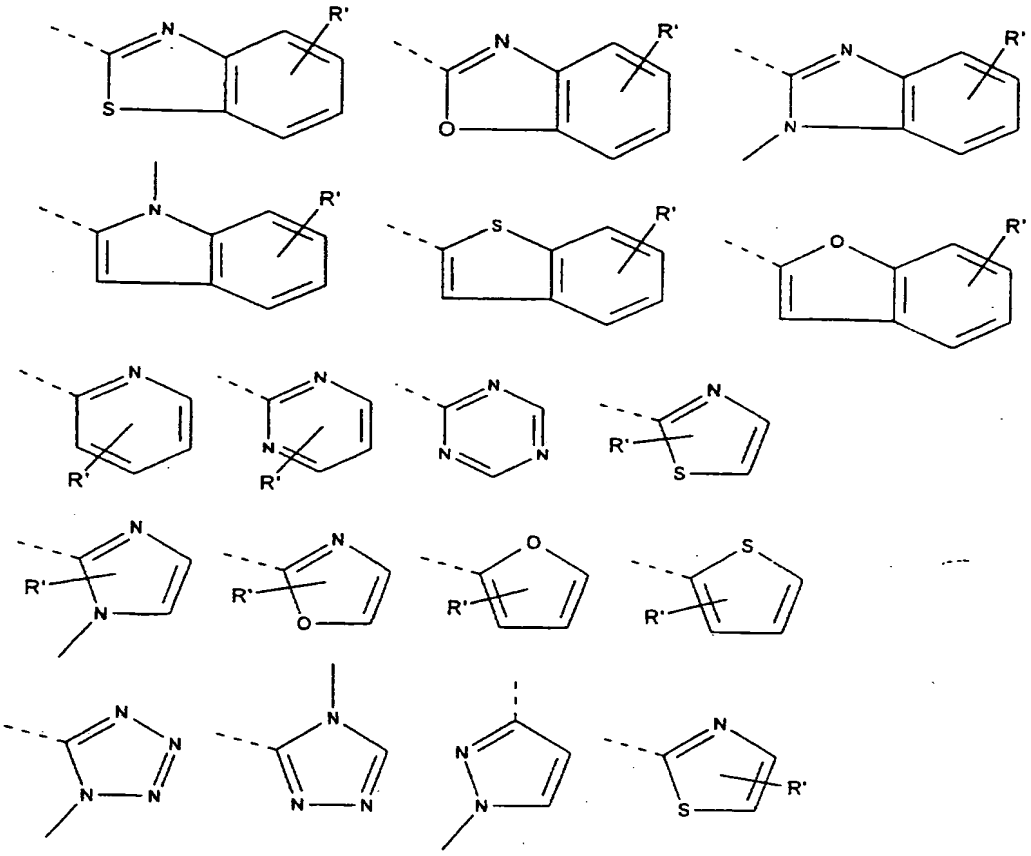
wherein

X_5, X_{10}, X_{11} and X_{12} are each independently selected from the group consisting of N, or C-X_7 where X_7 is hydrogen, C_{1-4} alkyl, or C_{5-8} aryl;

X_6 and X_{13} are each independently selected from the group consisting of C, O, N, S, N-X_7, or CH-X_7; and

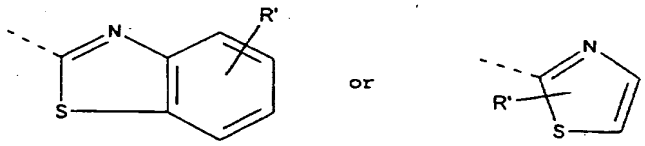
R' is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

5. A compound according to claim 4, wherein T is selected from the group consisting of:



wherein R' is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

6. A compound according to claim 5, wherein T is selected from:



wherein R' is hydrogen, C_{1-16} alkyl optionally carboxyl substituted, carboxyl, -C_{0-16} alkyl-CO_2-C_{1-16} alkyl, C_{6-20} aralkyl, C_{3-7} cycloalkyl, aryl or an aromatic heterocycle.

7. A compound according to claim 1, wherein one of W and X is N-R_4; and
R_4 is a hydrophobic group selected from C_{1-20} alkyl, C_{2-20} alkenyl or C_{2-20} alkynyl optionally interrupted by a carbonyl group, C_{6-16} aryl, C_{3-7} cycloalkyl, C_{6-20} aralkyl, C_{6-20} cycloalkyl substituted C_{1-20} alkyl, wherein the aliphatic portion is optionally interrupted by a carbonyl group and the ring portion is optionally substituted with C_{1-6} alkyl; and a hydrophobic amino acid side chain.

8. A compound according to claim 7, wherein one of W and X is CH_2.

9. A compound according to claim 8, wherein W is CH_2; X is N-R_4 and Y is C=O or CH_2.

10. A compound according to claim 1, wherein R_2 and R_2' are both H.

11. A compound according to claim 1, wherein Q is C=O.

12. A compound according to claim 1, wherein Y is CH-R_4 or C-R_4 and R_3 and R_4 together with Y form a 5 or 6 member saturated or unsaturated carbocyclic ring.

13. A compound according to claim 12, wherein said carbocyclic ring is a phenyl ring.

14. A compound according to claim 1, selected from:
(1) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide;
(2) N-[1-(benzothiazole-2 carbonyl)-4-guanidino-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-piperazin-1-yl]-acetamide;
(3) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide; (4) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-4-phenylmethanesulfonyl-

piperazin-1-yl)acetamide;

(5) N-[1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-{4-[(3,4-dichloro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-acetamide;

(6) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl}-acetamide;

(7) N-[1-(4-amino-cyclohexyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl}-acetamide;

(8) N-[1-(3-carbamimidoyl-benzyl)-2-oxo-thiazol-2-yl-ethyl]-2-(2-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide;

(9) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-isopropyl-6-oxo-4-(3-phenyl-propyl)-piperazin-1-yl}-acetamide;

(10) 2-(2-benzyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-ylethyl]acetamide;

(11) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-isopropyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide;

(12) N-[1-(4-aminocyclohexyl)-2-thiazol-2-ylethyl]-2-(2-isopropyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide;

(13) N-[1-(4-aminocyclohexyl)-2-oxo-2-thiazol-2-ylethyl]-2-(2-benzyl-6-oxo-4-phenylmethanesulfonyl-piperazin-1-yl}-acetamide;

(14) N-[1-(4-aminocyclohexyl)-2-oxo-2-thiazol-2-ylethyl]-2-{2-benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-acetamide;

(15) 2-{2-benzyl-4-[3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-ylethyl]-acetamide;

(16) 2-(4-benzenesulfonyl-2-oxo-piperazin-1-yl)-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide;

(20) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-

acetamide;

(21) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-methyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(22) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-isopropyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(23) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-isobutyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(24) 2-[2-sec-Butyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;

(25) 2-[2-Butyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(26) 2-{2-Benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(27) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[3,6-dioxo-4-(3-phenyl-propyl)-2-pyridin-3-ylmethyl-piperazin-1-yl]-acetamide;

(28) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(29) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[3-(4-chloro-benzyl)-2,5-dioxo-1-(3-phenyl-propyl)-piperidin-4-yl]-acetamide;

(30) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(31) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-cyclohexylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(32) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-

thiazol-2-yl-ethyl]-2-[2-(4-methoxy-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(33) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(34) N-[2-Benzothiazol-2-yl-1-(3-carbamimidoyl-benzyl)-2-oxo-ethyl]-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(35) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-methoxy-N-methyl-propionamide;

(36) 2-[2-Benzhydryl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(37) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[3,6-dioxo-2-phenethyl-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(38) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(39) N-(1-Formyl-4-guanidino-butyl)-2-[2-(4-methoxy-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(40) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(4-chloro-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide;

(41) N-[2-Benzothiazol-2-yl-1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(42) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-piperidin-1-yl-ethyl]-acetamide;

(43) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-methyl-propionamide;

(44) 2-{2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-

piperazin-1-yl]-acetylamino}-3-(1-carbamimidoyl-piperidin-3-yl)-N-cyclopentyl-propionamide;

(45) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(hydroxy-thiazol-2-yl-methyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(46) 2-{2-Benzyl-4-[3-(3,4-dichloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(47) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(48) 2-(2-Benzyl-3,6-dioxo-4-phenethyl-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(49) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(2,4-dibenzyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(50) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(2,4-dibenzyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(51) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-hydroxymethyl-ethyl]-acetamide;

(52) N-[1-(1-Carbamimidoyl-piperidin-4-yl)-2-oxo-2-thiazol-2-yl-ethyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(53) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-(4-methyl-2-naphthalen-1-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(54) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(55) 2-{2-Benzyl-4-[3-(4-methoxy-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-

piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(56) 2-[2-Benzyl-3,6-dioxo-4-(3-p-tolyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(57) 2-{2-Benzyl-4-[3-(4-chloro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(58) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-4-yl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;

(59) N-[1-Benzoyl-2-(1-carbamimidoyl-piperidin-3-yl)-ethyl]-2-(2-benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(60) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-phenyl-ethyl]-acetamide;

(61) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;

(62) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;

(63) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;

(64) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;

(65) 2-{2-Benzyl-4-[3-(4-nitro-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(66) 2-[2-Benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;

(67) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-propyl]-acetamide;

(68) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(4-methoxy-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide;

(69) 2-(4-Benzyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(70) 2-[2-Benzhydryl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(71) 2-{2-Benzyl-4-[3-(4-isopropyl-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(72) 2-{2-Benzyl-4-[3-(4-hydroxy-phenyl)-propyl]-3,6-dioxo-piperazin-1-yl}-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(73) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(74) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-4-methyl-3,6-dioxo-piperazin-1-yl]-acetamide;

(75) N-[4-(N-Methyl-guanidino)-1-(thiazole-2-carbonyl)-butyl]-2-(4-methyl-2-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-yl)-acetamide;

(76) 2-[4-Butyl-2-(3,4-dichloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(77) 2-(2-Benzyl-4-butyl-3,6-dioxo-piperazin-1-yl)-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(pyridine-2-carbonyl)-ethyl]-acetamide;

(78) N-[2-(1-Carbamimidoyl-piperidin-3-yl)-1-(pyridine-2-

carbonyl)-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(79) N-[1-(1-Carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(4-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(80) 2-[4-Butyl-3,6-dioxo-2-(phenylmethanesulfonylamino-methyl)-piperazin-1-yl]-N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(81) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2,5-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(82) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[4-guanidine-1-(thiazole-2-carbonyl)-butyl]-acetamide;

(83) N-[2-benzothiazol-2-yl-1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-ethyl]-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(84) N-[2-(1-carbamimidoyl-piperidin-3-yl)-1-(thiazole-2-carbonyl)-ethyl]-2-[2-naphthalen-2-ylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(85) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-thiazol-2-yl-ethyl]-2-[2-methyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(86) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-[2-(3-carbamimidoyl-phenyl)-1-(thiazole-2-carbonyl)-ethyl]-acetamide;

(87) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(3-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(88) 2[4-butyl-2-(3,4-dichloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2yl-ethyl]acetamide;

(89) N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-[2-(3,4-dichloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperzin-1-yl]-acetamide;

(90) 2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-

oxo-2-thiazol-2-yl-ethyl]-acetamide;

(91) 2{2-[4-butyl-2-(2-chloro-benzyl)-3,6-dioxo-piperazin-1-yl]acetylamino}-3-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;

(92) 2-[4-benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-4-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide;

(93) 3-(1-carbamimidoyl-piperidine-3-yl)-2-[2-[2-(2-chloro-benzyl)-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetylamino]-N-methyl-propionamide;

(94) (3S)-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-2-{4-[3-(3,4-dichloro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-acetamide;

(95) 2-(4-Benzenesulfonyl-2-oxo-piperazin-1-yl)-*N*-[1-(benzothiazole-2-carbonyl)-4-guanidino-butyl]-acetamide;

(96) 4-{2-Carboxy-2-oxo-1-[2-(2-oxo-4-phenylmethane-sulfonyl-piperazin-1-yl)-acetylamino]-ethyl}-cyclohexylamine;

(97) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-piperazin-1-yl)-acetamide; (98) 5-[(2R)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazinan-1-ylmethyl-carboxamido]pentylamine; (99) 4-(2S)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazan-1-ylmethyl-carboxamido]butylamine;

(100) 4-[(2R)-2-benzyl-3,6-dioxo-4-(3-phenylpropyl)-1,4-diazinan-1-ylmethyl-carboxamido]guanidinobutane;

(101) N-(4-carbamimidoyl-phenyl)-2-[2-cyclohexa-2,4-dienylmethyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]acetamide;

(102) N-(4-amino-cyclohexyl-methyl)-2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-acetamide;

(103) 2-[2-benzyl-3,6-dioxo-4-(3-phenyl-propyl)-piperazin-1-yl]-N-(1-carbozmimdoyl-piperidin-4-ylmethyl)-acetamide;

(104) *N*-(4-Amino-cyclohexyl-methyl)-2-[4-(diphenyl-methanesulfonyl)-2-oxo-piperazin-1-yl]-acetamide; and

(105) *N*-(4-Carbamimidoyl-benzyl)-2-[4-(diphenyl-methanesulfonyl)-2-oxo-piperazin-1-yl]-acetamide;

(106) 2-[4-Butyl-3,6-dioxo-2-(phenylmethanesulfonylamino-methyl)-piperazin-1-yl]-N-[1-(1-carbamimidoyl-piperidin-3-ylmethyl)-2-oxo-2-thiazol-2-yl-ethyl]-acetamide

(107) 2-{4-Benzyl-2-[(diphenyl-methanesulfonylamino)-methyl]-3,6-dioxo-piperazin-1-yl}-N-(1-carbamimidoyl-piperidin-4-ylmethyl)-acetamide;

(108) 2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-N-(1-carbamimidoyl-piperidin-4-ylmethyl)-acetamide;

(109) 2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-*N*-(4-carbamimidoyl-2-chloro-benzyl)-acetamide;

(110) *N*-(6-Amino-2-chloro-pyridin-3-ylmethyl)-2-[4-benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-acetamide; and

(111) {[4-({2-[4-Benzyl-2-(4-methoxy-benzyl)-3,6-dioxo-piperazin-1-yl]-acetylamino}-methyl)-2,5-dichloro-phenyl]-imino-methyl}-carbamic acid ethyl ester.

15. A compound according to claim 12, selected from:

(17) 2-(4-benzoyl-2-oxo-3,4-dihydro-2H-quinoxalin-1-yl)-N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-acetamide;

(18) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-[2-oxo-4-(3-phenyl-propionyl)-3,4-dihydro-2H-quinoxalin-1-yl]-acetamide; and

(19) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihyero-2H-quinoxalin-1-yl)acetamide

(112) N-[4-guanidino-1-(thiazole-2-carbonyl)-butyl]-2-(2-oxo-3,4-dihydro-2H-quinoxalin-1-yl)-acetamide;

(113) *N*-(4-Guanidino-butyl)-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihydro-2*H*-quinoxalin-1-yl)-acetamide; and

(114) *N*-(1-Carbamimidoyl-piperidin-4-ylmethyl)-2-(2-oxo-4-phenylmethanesulfonyl-3,4-dihydro-2*H*-quinoxalin-1-

yl)-acetamide.

16. A method for the treatment or prophylaxis of thrombotic disorders in a mammal, comprising administering to said mammal an effective amount of a compound according to claim 1.

17. A method according to claim 16, wherein said thrombotic disorder is venous thrombosis.

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18. A method according to claim 16, wherein said thrombotic disorder is a pulmonary embolism.

19. A method according to claim 16, wherein said thrombotic disorder is arterial thrombosis.

20. A method according to claim 16, wherein said thrombotic disorder is myocardial infarction.

20 21. A method according to claim 16, wherein said thrombotic disorder is cerebral infarction.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 97/15312

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/078 C07K5/097 C07K5/023 A61K38/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	WO 96 18644 A (CORVAS INT INC ;TAMURA SUSAN YOSHIKO (US); SEMPLE JOSEPH EDWARD (U) 20 June 1996 see the whole document ---	1-21
X,Y	WO 95 35313 A (CORVAS INT INC ;SEMPLE JOSEPH E (US); LEVY ODILE E (US); NUTT RUTH) 28 December 1995 see the whole document ---	1-21
X,Y	WO 95 35311 A (CORVAS INT INC ;SEMPLE JOSEPH EDWARD (US); ARDECKY ROBERT J (US);) 28 December 1995 see the whole document ---	1-21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
1 December 1997	12. 12. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 97/15312

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 19491 A (IAF BIOCHEM INT ;GILLARD JOHN (CA); DIMAIO JOHN (CA); SIDDIQUI M A) 27 June 1996 see the whole document ---	1-21
Y	WO 96 19483 A (IAF BIOCHEM INT ;DIMAIO JOHN (CA); SIDDIQUI M ARSHAD (CA); GILLARD) 27 June 1996 see the whole document ---	1-21
X	US 5 120 718 A (GOLDMAN ROBERT C ET AL) 9 June 1992 see the whole document -----	1,2,7-9

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/15312

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/US 97/15312

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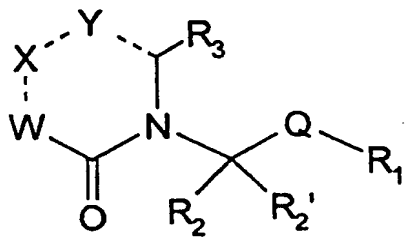
(54) Title: LACTAM INHIBITORS OF THROMBIN

(57) Abstract

This invention relates to heterocyclic inhibitors of the enzyme thrombin, their preparation, and pharmaceutical compositions thereof having general formula (I), wherein W, X, Y R_1 to R_3 are as defined herein. Also, the invention relates to the use of such compounds and compositions as anticoagulants and as agents for the treatment and prophylaxis of thrombotic disorders such as venous thrombosis, pulmonary embolism and arterial thrombosis resulting in acute ischemic events such as myocardial infarction or cerebral infarction.



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